

This English version of the Commission Decision is intended to be reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The FSCJ shall not be responsible for any consequence resulting from use of this English version.

Guidelines for the Risk Assessment of Food Additives for Fortification

Chapter 1: General Provisions

Article 1: Background

The Food Safety Commission of Japan (FSCJ) endeavors to establish guidelines for the assessment of food-related hazards on human health (hereinafter referred to as “the risk assessment”), based on “Basic Matters in Article 21 paragraph (1) of the Food Safety Basic Act” (the Cabinet Decision, June 29, 2012).

Accordingly, the following guidelines have been established: “Standards for the Safety Assessment of Genetically Modified Foods (Seed Plants)” (January 29, 2004), “Stance on Assessment of the Effect of Foods on Human Health Regarding Official Specifications of General Fertilizers” (March 18, 2004), “Standards for Safety Assessment of Food Additives Produced Using Genetically Modified Microorganisms” (March 25, 2004), “Stance on Safety Assessment of Genetically Modified Feeds and Feed Additives” (May 6, 2004), “Assessment Guideline for the Effect of Foods on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Animals” (September 30, 2004), “Standards for Safety Assessment of Genetically Modified Foods (Microorganisms)” (June 26, 2008), “Guideline for Assessment of the Effect of Foods on Human Health Regarding Food Additives” (May 27, 2010) (hereinafter referred to as “Guideline for Assessment of Additives”)¹⁾, and Guidelines for the Assessment of Flavoring Substances in Foods on Health (May 17, 2016).

Guidelines for risk assessment are essential for securing the scientific validity and fairness of assessments as well as for clarifying the data required for application, keeping the transparency of assessment both within and outside Japan.

The risk assessment of food additives, including those for fortification such as vitamins and minerals, has been currently conducted according to the Guideline for Assessment of the Effect of Foods on Human Health Regarding Food Additives. The risk assessment of the food additives for fortification (hereinafter referred to as “FAF”), however, need to be conducted, taking the following characteristics into consideration. First, internationally these substances are not necessarily categorized as food additives. In addition, it should be taken into account that these substances are also nutrients, and therefore an approach from

conventional toxicology may not be applicable for the risk assessment. Moreover, for establishing Upper Intake Level, recommended dietary allowance (RDA) and adequate intake (AI) determined in “Dietary Reference Intakes for Japanese” (the public notice of the Ministry of Health, Labour and Welfare, Notification No.199 of 2015. Hereinafter referred to as “Dietary Reference Intakes for Japanese (2015)”²⁾ need to be considered.

Recently, a study entitled “Study on the Procedure for the Risk Assessment of Food Additives for Fortification and Processing Aids in Japan” (Principal Investigator: Takashi Umemura, National Institute of Health Science) was conducted with the support of a FSCJ grant for the Research and Survey Program. The study summarized the draft guidelines for the risk assessment of FAF⁵⁾, taking into account the results of the previously conducted risk assessments of FAF, “A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances Report of a Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment”³⁾, and the survey report⁴⁾ on approaches for risk assessment of FAF employed in the Joint FAO/WHO Expert Committee on Food Additives (JECFA), U.S. Institute of Medicine^{*1} Food and Nutrition Board (IOM/FNB), European Food Safety Authority (EFSA), and other organizations.

FSCJ finalized the new guidelines for the risk assessment of FAF based on the research report by Umemura’s group. Thus, the risk assessment of FAF is conducted according to these guidelines from now on.

The guidelines would be revised after reviewing their provisions, taking into account international trends of assessment guidelines and new scientific findings both within and outside Japan, if needed.

Article 2: Definition

1. FAF: Food additives for fortification

FAF are “food additives” that are used for improving nutritional status such as vitamins and minerals. “Food additives” are defined in Article 4, paragraph (2) of the Food Sanitation Act (Law No. 233 of 1947) as substances which are used by being added, mixed, or infiltrated into food or by other methods in the process of producing food or for the purpose of processing or preserving food. Vitamins and minerals refer to the substances determined in “Dietary Reference Intakes for Japanese (2015)” specified by the Minister of Health, Labour and Welfare, including the related substances^{*2}.

2. ULadd: Upper Intake Level for Addition

ULadd is, for the purpose of the risk assessment of FAF, the maximum level of the long-term average daily intake from non-dietary sources judged to be unlikely to lead to adverse health effects in humans. “Tolerable Upper Intake Level (UL)” refers to the

*1 The present name is National Academy of Medicine (NAM).

*2 The term “related substances” refers to substances of which evaluation, along with the evaluation of the target substances, is considered to be scientifically appropriate. These include mineral compounds consisting of different base moiety, vitamin derivatives, and metabolites of the target substances, for example.

maximum level of the long-term average daily intake from all sources judged to be unlikely to lead to adverse health effects in humans.

3. NOAEL : No-observed-adverse-effect level

The NOAEL is the highest dose of a substance that causes no detectable adverse effect, found by toxicity study under defined conditions of exposure. This definition is also applied to the interpretation of human data.

4. LOAEL : Lowest-observed-adverse-effect level

The LOAEL is the lowest dose of a substance that causes a detectable adverse effect, found by toxicity study under defined conditions of exposure. This definition is also applied to the interpretation of human data, but a value of LOAEL could be determined based on the case report as well.

5. Endpoint

Endpoint is an observable or measurable biological event and chemical concentration etc. which are used as an indicator of exposure effects of the target substance.

6. HOI: Highest Observed Intake

The HOI is the highest intake in human as reported, within studies of acceptable quality (including intervention studies), survey on the amount of intake, etc. In these guidelines, HOI in principle is derived only when no adverse health effects have been identified^{*3}.

7. ADI: Acceptable Daily Intake

The ADI is a measure of the amount of a specific substance that is ingestible on a daily basis over a lifetime assumingly without adverse health effects based on the current scientific knowledge.

8. UF: Uncertainty Factor

UF is a factor used to consider further uncertainty in calculating ULadd etc. from NOAEL or LOAEL for a specific substance. Also, a factor used to consider further safety in calculating ADI etc. from NOAEL or LOAEL is called Safety Factor (SF).

Article 3: Purpose

The purpose of the guidelines is to establish the guiding principle of risk assessment on food additives for fortification that are classified as additives and to define the scope of required documents. The risk assessment is to be conducted for cases in which the Minister of Health, Labour and Welfare (MHLW) specifies as having no risk to human health as provided in Article 10 of the Food Sanitation Act, or where MHLW intends to establish standards or specifications in accordance with the provisions of Article 11, paragraph (1) of the Act, or where MHLW hears the Commission's opinions if they are

^{*3} Internationally, the explanation of the HOI was described in FAO/WHO. (2006) (p.113)³⁾

recognized as necessary for formulating policies to ensure food safety in accordance with Article 24, paragraph (3) of the Food Safety Basic Act (Act No.48, 2003).

Article 4: Approach for the Risk Assessment

The following approaches are to be taken for assessments, in addition to the description in Chapter 2.

1. Evaluation of safety shall be conducted preferably based on the data from human studies than those from animal studies as much as possible.

In the case where human data in specific life stages such as childhood, pregnancy, and lactating period are unavailable, animal studies are considered to be useful for qualitative evaluation such as assumption of mechanism for adverse effects or examination of reliability of the biomarker, etc., and therefore, animal studies shall be evaluated as necessary.

2. The risk assessment in particular populations, such as infants, children, pregnant women, lactating women, and the elderly (hereinafter referred to as subpopulation^{※4}), shall be conducted as necessary. When data suggesting potential risks in subpopulations are available, these data shall be considered.
3. Characteristics or toxicokinetics of the target substance should be fully taken into consideration in the evaluation. If necessary, data on the related substances^{※2} shall be considered.
4. It is desirable to consider the use of *in-vitro* studies that are widely conducted in other fields such as drug development and recommended to be employed in the risk assessment of a FAF, if needed. For example, the *in-vitro* data obtained using human cultured cells or using human metabolic enzymes may be extrapolated to humans in case the adverse effects from the metabolites are of a concern in animal studies.
5. Points relevant to an interaction of the assessed item with pharmaceuticals shall be studied if needed when there is any information that may suggest risks from such an interaction.
6. Concerning degradation products of FAF, mixed impurities and human specific metabolites, necessity of the evaluation shall be examined. Stability of FAF, including stability in food, shall be also examined. If not stable, types and amounts of major degradation products shall be characterized.
7. Studies using methods that are scarcely employed currently in JECFA and in FSCJ, such as studies in genetically modified animals, have to be considered carefully.

^{※4} In Table 7-2 on p.106 of FAO/WHO (2006)³, “subpopulation” is used as follows: “For what subpopulations are there sufficient data to establish a UL?” and “Examine data for groups such as children of different ages, pregnant women, young adults.”

Article 5: Approach for the Documents Required

The approach and points to be considered regarding the documents required are as follows, in addition to the description in Chapter 2.

1. Responsibility of applicants

Applicants are to submit documents relevant to the evaluation on their own responsibility, and the applicants should also secure reliability of the provided information.

2. Additional documents for evaluation

Evaluation in principle shall be conducted using the documents submitted by the applicant. If the documents are considered insufficient for evaluation, the applicant shall be asked for additional documents.

3. Omission of documents for evaluation

When the target substance is a related substance of other FAF which is already designated, and if there are scientific rationales and rationales are clearly described, a part of the studies may be omitted.

4. Points to be considered in the amendment of standards for use or specifications

(1) The following points shall be considered in the amendment of standards for use.

(a) For the amendment of standards for use of a FAF of which risk assessment by FSCJ is already completed applicants shall submit documents concerning the estimation of the daily intake of the FAF considering requested addition of foods in which the additive is to be used or considering changes in the amount of use of the additive. Even in this case, applicants shall also submit documents regarding new toxicological findings, if any.

(b) When the risk assessment of the additive of the subject matter not yet completed by FSCJ, applicants in principle shall submit documents required for the evaluation.

(2) For the amendment of specifications, applicants need to demonstrate the validity of amended specifications and describe that the amendment requested would not raise issues of the safety of the additive of the subject matter

5. Test guidelines

Practical procedures of each study are recommended to follow the test guidelines that are approved internationally, such as those of the Organisation for Economic Co-operation and Development (OECD).

6. Reliability of documents

As documents required for the evaluation, applicants in principle shall provide the following: data of studies conducted using a method with secured reliability at an adequately administered test facility such as a GLP-conforming test facility; risk assessment reports from the international organisations; and scientifically reliable articles. As for data suggesting safety concern of the FAF, however, applicants shall

provide the data irrespective of the reliability because such information may be necessary for evaluating the FAF.

7. Autopsy and histopathological evaluation

FSCJ recommends performing autopsy and histopathological evaluation by experienced experts.

8. Raw data and specimens

Applicants shall keep existing raw data and specimens from animal studies used for the request for a period designated in GLP or until the evaluation becomes complete, being ready to provide them as necessary.

Article 6: Re-evaluation

Potential adverse effects of FAF need to be observed continuously even in the case of an approved additive. If potential adverse effects of such an additive are suggested by a progress of science and technology, re-evaluation of the additive should be conducted.

When important data are newly acquired that cause doubts about the safety of additives evaluated in the past, re-evaluation of the additive for fortification should be conducted immediately.

Chapter 2: Detailed exposition

The detailed exposition of approach for the assessment is described in this Chapter. Information required for the assessment is as follows:

1. Outline of the target substance.
2. Data relevant to safety. (toxicokinetics, human study and toxicity study)
3. Estimation of Daily Intake.

Article 1: Outline of the Target Substance

1. Name and usage
2. Origin or history of discovery
3. Usage in Japan and other countries (related substances included)
4. Risk assessments by Japanese and international organizations (related substances included)
5. Physicochemical properties

Chemical name (generic names in Japanese and English, CAS number), molecular formula, molecular weight, molecular structure, manufacturing method, property, stability (in food included), draft specifications, etc.

6. Draft standards for use

(1) When setting relevant standards for use is considered necessary for specifying subject foods for use and the amount of use, etc. based on the comprehensive evaluation of safety and efficacy of the FAF, rationales for setting the standards for use need to be clarified. In setting the standards, the results of comparison of the estimated daily intake^{※5} (EDI) (refer to Article 3) with the estimated ULadd etc. shall be taken into consideration.

(2) When setting the standards for use is considered unnecessary, rationales for the consideration need to be clarified.

7. Others (information useful for the risk assessment)

Article 2: Information relevant to safety

1. Toxicokinetics

(1) When toxicokinetics of a substance is evaluated, the data from human study shall be preferably considered in principle because of presumable difference between human and animals in nutritional requirement and absorption. However, when available human data on toxicokinetics of the substance are insufficient for evaluation, the toxicokinetics in human shall be presumed based on the animal study in a species that is scientifically adequate for such presumption or based on the data of *in vitro* study using cultured human cells. In addition, the data from animal studies may be used for presumption of detailed toxicokinetics mechanisms or of adverse effect occurrence, or for selection of a biomarker. When a final evaluation is concluded based on the data from animal study, toxicokinetics data in the animal species used for toxicity evaluation shall be taken into consideration. The animal studies shall be conducted in accordance with “1. Toxicokinetics study” in Article 2 of Chapter 2 of “Guideline for the Assessment of the Effect of Food Additives on Health”.

(2) Because chemical structures^{※6} of FAF may affect utilization or adverse effects, similarity and difference in the metabolism and action of the target substance due to the chemical structure need to be studied.

(3) The risk assessment in subpopulation shall be conducted if necessary. If toxicokinetics data in each subpopulation are available, these data will be also taken into consideration.

2. Information from human studies^{※7}

Information from human studies, such as the evidence table, case reports and meta-analysis, shall be summarized and evaluated according to (1) to (3). The NOAEL and LOAEL shall be also described with the rationales for the determination and consideration. When NOAEL or LOAEL cannot be determined, data for considering HOI will be required.

※5 Both intake from habitual meal and that from additives in food shall be considered.

※6 Isoforms of vitamins etc. are examples.

※7 Categorization of effects in human and preparation of the evidence table in this paragraph referred the approach in FAO/WHO (2006)³. The relevant part of FAO/WHO (2006)³ is shown in Appendix 2.

(1) Effects in humans: (Category 1~7)

The measurable effects of FAF intake within the causal pathway of an adverse health effect can range from biochemical changes without functional significance to clinical effects that signify irreversible impairment of organ function. Therefore, setting the following seven categories for the effects of FAF in humans, each effect of the target substance shall be categorized^{*8}.

1. Biochemical changes within the homeostatic range and without indication of adverse sequelae^{*8}
2. Biochemical changes outside the homeostatic range without known sequelae
3. Biochemical changes outside the homeostatic range that represent a biomarker of potential adverse effects due to excess
4. Clinical features indicative of a minor but reversible change
5. Clinical features of significant but reversible effects
6. Clinical features indicative of significant but reversible organ damage
7. Clinical features indicative of irreversible organ damage

In accordance with this categorization, changes categorized as Category 3 and above will be considered to be adverse effects for specifying ULadd etc. of the target substance. If sufficient data are available, however, changes categorized as Category 2 may be adverse effects for specifying ULadd etc. of the target substance.

(2) Preparation of the evidence table etc. (Category A~C)

The data obtained from human studies shall be summarized in terms of the following points, and the evidence table with the summarized data shall be prepared.

In a description regarding the endpoint of the survey, assessment reports from international organizations etc. may be referred.

- Subjects' age, sex, health, race/ethnic background
- Size of study
- Nature of nutrient substance studied
- Range of intakes
- Duration of intakes
- Intakes from background diet and those from (as applicable) food, supplements, and water

^{*8} The term "adverse sequelae" is used in FAO/WHO (2006) (p.30).

- Intake assessment method (s)
- Endpoints investigated
- Relationship between intake and response (i.e. adverse health effect)
- Nature of critical adverse health effect (validation and quality criteria for the selected endpoint, i.e. biomarker of effect or clinically observable effect)
- Effect size (relationship with intake, subpopulations (infants, children, pregnant women, lactating women, and elderly), and other factors)
- Confounders (e.g. use of medications) and effect modifiers (e.g. susceptibility)
- Study design (RCT, cohort study, case-control study, etc.)
- Category (1~7) of the assessed effect in humans.
- Scientific standard of the study (Category A ~ C)

The studies summarized in the evidence table should be categorized into the following A ~ C on the basis of its study design and quality^{*9}.

Meta-analysis and case reports are not subject of the evidence table, but should be summarized separately.

A: A study with a quality above certain level, with a study design where contingency, bias, and confounders are adequately controlled (e.g. study conducted by randomized controlled trial (RCT) or double blind test.)

B: A study with a quality above a certain level, with a study design where contingency, bias, and confounders are almost controlled. (e.g. cohort study and case-control study)

C: A study that comes under neither A nor B

(3) Determination based on the information from human studies.

It is often difficult to determine an adverse effect on human health based on a single finding. Therefore, when a conclusive NOAEL or LOAEL is determined based on the abovementioned (1) and (2), multiple findings, if available, need to be assessed comprehensively in addition to considering scientific quality of each finding. Findings relevant to meta-analysis shall be respected.

^{*9} Categorization into A to C shall be conducted taking the following points into consideration.

- Are subpopulation, subjects, setting, intakes, and comparison groups clearly described?
- Is the size of the study appropriate?
- Are the results measured appropriately?
- Is the report based on the study processed with appropriate statistical and analytical method?
- Is there a clear description on dropouts?
- Is the intake assessment conducted appropriately?

Endpoint that is judged to have causal relationship in those reports shall be investigated referring assessment reports from international organizations or other documents. Regarding the endpoint, whether NOAEL or LOAEL in each finding can be determined or not shall be investigated, and NOAEL or LOAEL shall be determined considering the Category A) to C) which are set in the evidence table prepared according to the procedure (2).

In addition, some factors such as racial and ethnic background and region may be effect modifiers, so assessment should be conducted taking these factors into account in addition to the scientific quality of findings that is categorized into A) to C) in the procedure (2), such as study design and contents of results.

When NOAEL or LOAEL cannot be determined based on human studies, HOI should be considered as estimate of safe level. In these guidelines, the following values are used in principle as HOI for a dose administered to healthy groups or for observed intake considering distribution of intake and others: the maximum intake in an intervention study, or the 99th or 95th percentile in an observational study or in a study on intake.

Assessment shall be conducted on subpopulations, if necessary. When there are findings of adverse effects in each subpopulation, such findings shall also be considered.

3. Toxicity study

In principle, animal studies on adverse health effects shall be conducted in accordance with “2. Toxicity study” in Article 2 of Chapter 2 of “Guideline for Assessment of Additives”. Assessment shall be conducted on subpopulations, if necessary. When there are findings of adverse health effects in animals that correspond to each subpopulation, such findings shall also be considered. It is to note that methods to set control group in animal studies may be different between a study on FAF and that on non-nutritional components.

Article 3. Estimation of Daily Intake

Daily intake in Japan shall be estimated, with care for avoiding underestimation, as follows. In principle, the daily intake shall be estimated as the sum of daily intake of the target substance through the food subject^{※10} and daily intake of the same nutrient (composing FAF) from foods as a background, where the daily intake through the food subject is calculated by multiplying the daily intake of the food subject by the concentration of the target substance.

When the estimation includes intake from food etc., not only the mean value but also the median and distribution need to be considered. The maximum value of intake is to be considered as well. Daily intake of a food shall be estimated appropriately based on the daily intake of each food group reported in the National Health and Nutrition Survey or other documents. For daily intake of FAF, estimation may be conducted based on the data obtained by reliable methods such as market basket investigation or production statistics. Body weight used for the estimation shall be the average body weight designated in the latest decision of FSCJ.

※10 The food products in which the food additive can be used

Article 4. Risk Assessment

1. Fundamental of risk assessment is comprehensive evaluation based on findings in humans and estimated daily intake. Basically, setting of ULadd etc. should be done on the basis of NOAEL or LOAEL determined by findings in humans.
2. When an adverse health effect on humans due to intake of nutrient can be specified and NOAEL or LOAEL can be determined, ULadd etc. is to be set taking into account the identified adverse health effects or estimated daily intake. When NOAEL or LOAEL cannot be determined in human studies, evaluation may be conducted using HOI along with animal data. If HOI is higher than the value obtained from NOAEL in animal studies by applying appropriate factor such as uncertainty factor, HOI is basically used for a basis of setting ULadd etc. If HOI is lower than the value obtained from NOAEL in animal studies in the same way, it shall be considered whether the adverse health effects in animal studies that give a base for NOAEL can be extrapolated to humans, and the risk assessment shall be comprehensively conducted. It is not necessary, however, to specify ULadd etc. if sufficient data are available and also no adverse health effect is observed in human studies and animal studies.
3. However, even if the intake of the target substance is larger than HOI, it does not cause adverse health effects immediately. Thus, it is to note that the ULadd etc. specified on the basis of HOI are different indexes from those determined based on NOAEL or LOAEL, and are considered to be generally lower than those determined based on NOAEL or LOAEL. If the ULadd is determined based on HOI, that fact should be specified.
4. For specifying ULadd etc., the following considerations shall be required. a) Appropriate factors such as uncertainty factor should be applied, b) background factors and variability of scientific quality of the findings need to be considered, c) the data obtained from meta-analysis should be regarded as of importance, and d) the scientific quality of the findings evaluated in “2. Information from human studies” of Article 2 of Chapter 2 should be considered as the basis. In addition, it is to note that the range of requirement^{*11} in humans or estimated daily intake is often relatively close to NOAEL or LOAEL reported in humans.
5. If an evaluation of effect of chemical structures on the utilization or adverse effects, conducted as is described in “1. Toxicokinetics” of Article 2 of Chapter 2, reveals the scientific evidence which clearly shows a large difference between different chemical structures, ULadd etc. shall be specified distinctively for each structure. In other cases, efficiency (international unit; IU) or equivalent amount shall be considered for evaluation as necessary.
6. If tolerable upper intake level (UL) is specified for an additive for fortification in Dietary Reference Intakes for Japanese (2015) by the MHLW, the value and the background data shall be considered.
7. Evaluation on the subpopulations shall be conducted desirably based on findings in humans of each subpopulation regarding the findings as of importance. If particular

^{*11} In Dietary Reference Intakes for Japanese (2015), terms such as “estimated average requirement (EAR)”, “recommended dietary allowance (RDA)”, or “adequate intake (AI)” are used.

evidence is unavailable, however, difference between the subpopulations is evaluated based on findings from animal studies.

8. When ADI is specified based on the evaluation of animal data, the approach should follow “Guideline for Assessment of Additives” of Article 7 of Chapter 1.

Appendix 1 : Abbreviations

Abbreviation	Explanation
CAS	Chemical Abstracts Service
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization
FNB	Food and Nutrition Board
GLP	Good Laboratory Practice
HOI	Highest Observed Intake
IU	International Unit
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	Lowest Observed Adverse Effect Level
NAM	National Academy of Medicine
OECD	Organization for Economic Co-operation and Development
RCT	Randomized Controlled Trial
SF	Safety Factor
UF	Uncertainty Factor
UL	Tolerable Upper Intake Level
ULadd	Upper Intake Level for addition
WHO	World Health Organization

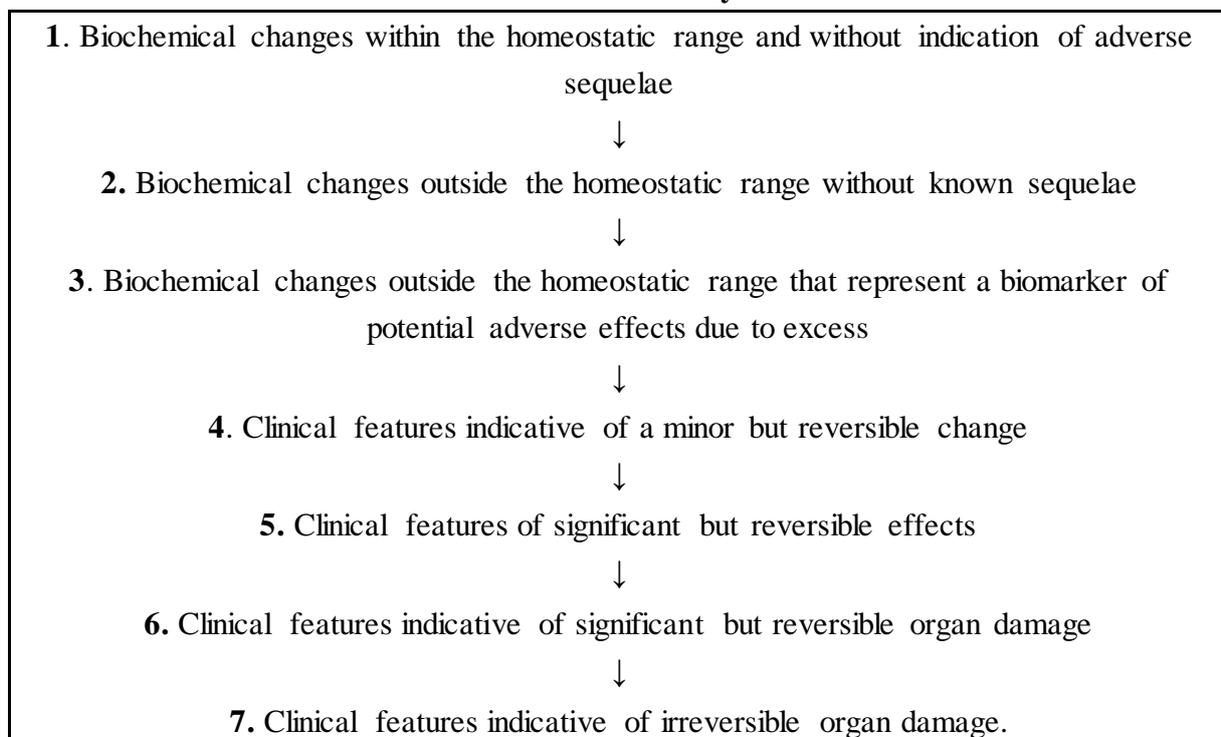
Appendix 2: Corresponding description in FAO/WHO³⁾

Category 1 to 7 of effects in humans (p. 29)³⁾

The measurable effects of high nutrient substance intake within the causal pathway of an adverse health effect can range from biochemical effects without functional significance (e.g. certain changes in enzyme activity) to clinical effects that signify irreversible impairment of organ function. Figure 3-3 shows the sequence of the observable effects—from initial non-specific biochemical changes to clear irreversible clinical outcomes (Renwick et al., 2004).

This flow diagram is generic in nature. In practice, the process of specifying the sequential measurement of the development of an adverse health effect would need to be developed for each type of adverse health effect. That is, the sequence would have to be fully characterized for each endpoint. For example, the sequential series of effects would need to be mapped separately for bone health effects, for liver damage, or for disorders of substrate metabolism.

Figure 3-3. Identifying Adverse Health Effects: Sequence of 'effects' in increasing order of severity



Note: Adapted from Renwick et al., 2004; 'features' includes signs and symptoms

Preparation of the evidence table (Categorization into A to C) (p. 45)^{4,5)}

In addition to extracting specific information as described above, one can assign a single overall quality grade to each study: e.g. either A, B, or C. Box 4-2 lists useful categories for a single summary rating of study quality. This approach provides a generic rating system for study quality that is applicable to each type of study design but does not replace the multi-component rating suggested above. Variations of this approach are widely used by many healthcare technology assessment organizations.

Box 4-2. Recommendations for Practice: Useful categories for specifying a single summary rating of study quality
<p><i>A: Least bias, results are valid.</i> A study that mostly adheres to the commonly held concepts of high quality for the particular level of study design; clear description of the (sub)population or study subjects, setting, intakes, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; clear reporting of dropouts; and no obvious bias.</p> <p><i>B: Susceptible to some bias, but not sufficient to invalidate the results.</i> A study that does not meet all the criteria in category A. It has some deficiencies but none likely to cause major bias. Study may lack information—thus making assessment of the limitations and potential problems difficult.</p> <p><i>C: Significant bias that may invalidate the results.</i> A study with serious errors in design, analysis, or reporting. These studies may have large amounts of missing information or discrepancies in reporting.</p>

Examples of information to be listed in the evidence table (p. 48)³⁾

4.2.4 Summarizing and presenting results

The identification of candidate adverse health effects sets the stage for the selection of the critical adverse health effect, which, in turn, serves as the basis for deriving a UL and allows characterization of the hazard. The risk assessor provides data concerning adverse health effects in a coherent summary, evaluates and rates studies, and presents meaningful information in summary form.

Overall, the summary from the nutrient substance hazard identification process contains all relevant information and documentation on the approaches used. At a minimum, the presentation of findings should include a summary description that includes the information listed in Box 4-4.

Box 4-4. Information Important to the Review of Individual Studies

- Subjects' age, sex, health, race/ethnic background (or, in the case of animal studies, species and strain)
- Size of study
- Nature of nutrient substance studied
- Range of intakes
- Duration of intakes
- Background diet and intakes from (as applicable) food, supplements, and water
- Intake assessment method(s)
- Characteristics of the nutrient substance studied
- Endpoints investigated
- Relationship between intake and response (i.e. adverse health effect)
- Nature of critical adverse health effect (validation and quality criteria for the selected endpoint, i.e. biomarker of effect or clinically observable effect) and why selected
- Effect size (relationship with intake, subgroups, other factors)
- Confounders (e.g. susceptibility, use of medications) and effect modifiers

References

1. Guideline for Assessment of the Effect of Foods on Human Health Regarding Food Additives” (May 27, 2010) (in Japanese)
2. Dietary Reference Intakes for Japanese. the Ministry of Health, Labor, and Welfare. Notification No 199. (March 31, 2015) (in Japanese)
3. A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances Report of a Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment, WHO Headquarters, Geneva, Switzerland, 2-6 May 2005, Report issued on 13 January 2006.
4. Report on “The Survey and Research on the Development of Methods for the Risk Assessment of Additives Regarding Processing Aids (food disinfectants, enzymes and extractants), and additives for fortification. By Mitsubishi Chemistry Technoresearch, March 2015.
5. A research on methods for assessment of the effect of foods on human health, “Study on the Procedure for the Risk Assessment of Food Additives for Fortification and Processing Aids in Japan”. By Takashi Umemura et al., (Res. No. 1502) (March 2016) (in Japanese)