**Provisional translation**

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Expert Committee on Feeds, Fertilizers, etc.

Food Safety Commission of Japan



# Guidelines for the Risk Assessment of Feed Additives

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## Chapter 1: General Provisions

### Article 1: Purpose

This set of Guidelines aims to define the scope of data required for risk assessment, to ensure consistency of evaluation methods between different hazards and respective categories of assessment, and to harmonize assessment approaches with international assessment standards to the extent possible. The intention is to maintain transparency and streamline the deliberative process for evaluation.

### Article 2: Definitions

For this set of Guidelines, the definitions of terminology listed below shall apply. General terminology used in this set of Guidelines aside from entries listed below are based on descriptions listed in the latest version of the Glossary Concerning Food Safety compiled by the Food Safety Commission of Japan (hereinafter referred to as “the FSCJ.”)

1. Feed
The term “Feed” as used in this set of Guidelines means feed as prescribed in Article 2, paragraph (2) of the Act on Safety Assurance and Quality Improvement of Feeds (Act No. 35 of 1953, hereinafter referred to as the “Feed Safety Act.”)

2. Feed Additive
The term “Feed Additive” as used in this set of Guidelines means Feed additive as prescribed in Article 2, paragraph (3) of the Feed Safety Act.

3. Formulation
The term “Formulation” as used in this set of Guidelines means Feed Additive whose specification or standard is as prescribed by the Minister of Agriculture, Forestry and Fisheries according to Article 3, paragraph (1) of the Feed Safety Act, which is directly added to Feed.

4. Technical Grade Active Ingredient
The term “Technical Grade Active Ingredient” as used in this set of Guidelines means raw material of Formulations that contain active ingredients (which also contain non-active ingredients.)

5. Excipient, etc.
The term “Excipient, etc.” as used in this set of Guidelines means substances that are ingredients of Formulations except for Technical Grade Active Ingredients, such as excipients, diluents, stabilizers, and others.

6. Risk Assessment Under Item (i)
The term “Risk Assessment Under Item (i)” as used in this set of Guidelines means risk assessment on the establishment of residue standards according to the provisions of Article 13, paragraph (3) of the Food Sanitation Act (Act No. 233 of 1947), which is conducted under a request for risk assessment based on the provisions of Article 24, paragraph (1), item (i) of the Food Safety Basic Act (Act No. 48 of 2003, hereinafter referred to as “the Act.”)

7. Risk Assessment Under Item (v)
The term “Risk Assessment Under Item (v)” as used in this set of Guidelines means risk assessment on the establishment, amendment or abolishment of specifications or standards of Feeds or Feed Additives under the provisions of Article 3, paragraph (1) of the Feed Safety Act, or the prohibition of manufacture, import, sale or use of Feed or Feed Additives under Article 23 of the same Act, which is conducted according to a request for assessment under Article 24, paragraph (1), item (v) of the Act.

8. Exempt Substance
The term “Exempt Substance” as used in this set of Guidelines means substances as prescribed by the Prime Minister that carry no apparent risk of adverse effects on human health under the provision of Article 13, paragraph (3) of the Food Sanitation Act.

9. Provisional Standard
The term “Provisional Standard” as used in this set of Guidelines means provisional residue standards established by the FSCJ without conducting risk assessments but taking into account standards by international organizations and national standards abroad following the introduction of the Positive List System and under the partial revision of Specifications and Standards for Food, Food Additives Etc. (Ministry of Health, Labour and Welfare, Notification No. 499 of 2005.)

**Article 3: Basic Policy for Dietary Risk Assessment of Feed Additives**

1. Principle for Assessment
Assessment of Feed Additives should be conducted scientifically and comprehensively based on information including biodisposition (pharmacokinetics), residue analysis results, toxicity study results, and usage status, etc., in light of intended use and properties.

2. Key Points to Note for Risk Assessment of Feed Additives
Risk assessments of Feed Additives are not conducted on the premise that humans would directly ingest the Feed Additives, but instead are conducted presuming cases in which humans would ingest food containing residual components and related substances from Feed Additives administered to livestock, etc.[1] Therefore, upon assessment of Feed Additives, it is generally important to take into account not only the toxicity of the components of the Feed Additives, but also human intake based on realistic scenarios of ingestion through food.

Inside the bodies of livestock, etc., components of Feed Additives may be metabolized or degraded into substances whose toxicities are either comparable to or surpassing the parent compounds. Hence, risk assessments of Feed Additives should incorporate evaluations of metabolites, etc., that may cause adverse effects on human health via ingestion of livestock or cultured fishery products as necessary, by means of comparing metabolisms across lab animals and livestock, etc., in addition to evaluating the parent compound components of Feed Additives.

3. Types of Risk Assessments of Feed Additives
Assessment of Feed Additives shall be conducted according to Risk Assessment Under Item (i), Risk Assessment Under Item (v), and Article 24, paragraph (1), item (xiv) of the Act under FSCJ Order (Cabinet Order No. 273 of 2003), and the Cabinet Office Ordinance prescribing the cases in which to issue the Cabinet Office Ordinance under FSCJ Order Article 1, paragraph (1) (Cabinet Office Ordinance No.66 of 2003, hereinafter referred to as "Ministerial Ordinance on Item (xiv)" )(Hereinafter referred to as "Risk Assessment Under Item (xiv)").

If such Formulations of Feed Additives subject to Risk Assessment Under Item (v) contain antimicrobial substances as active ingredients that are further deemed necessary to evaluate regarding the possibility and extent to which the antimicrobial-resistant bacteria selected by the use of said antimicrobial substance in livestock, etc., could affect human health via food ingestion, then additional assessment shall be conducted according to the Assessment Guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Animals (Decision of the FSCJ dated September 30, 2004).

Furthermore, regarding Feed Additives manufactured using genetic modification technology (hereinafter "GM technology"), which fall under Risk Assessment Under Item (xiv) according to the provisions of Ministerial Ordinance on Item (xiv), assessments shall be conducted under the Stance on Safety Assessments of Genetically Modified Feed and Feed Additives (Decision of the FSCJ dated May 6, 2004.)

4. Points to Bear in Mind Upon Conducting Risk Assessments
The Codex Alimentarius Commission laid down that "Risk assessment should incorporate the four steps of risk assessment, i.e., hazard identification, hazard characterization, exposure assessment and risk characterization" in its "Working Principles for Risk Analysis for Food Safety for Application by Governments" (CAC/GL 62-2007).

[1] In the Feed Safety Act, these are stipulated as cattle, pigs, chickens, honeybees, Japanese amberjack, red seabream, etc., as prescribed in Article 1 of the Order for Enforcement of the Act on Safety Assurance and Quality Improvement of Feeds (Cabinet Order No. 198 of 1976.)

In consideration of vastly different risk management situations per Feed, risk assessments on Feed Additives by the FSCJ shall be conducted following the risk assessment policy laid down by the Codex Alimentarius Commission to the extent possible, where for the time being, assessments shall be centered on hazard identification and hazard characterization based on the properties of components, etc., of the Feed Additive.

**Article 4: Policy for Required Documents Regarding Risk Assessment of Feed Additives**

1. Documents Required for Assessment
Since it is unreasonable to establish a uniform test method for all Feed additives, documents corresponding to the characteristics of each Feed Additive shall be used for assessment.

In principle, documents provided by risk management organizations deemed appropriate in light of scientific expertise shall be used for risk assessments. If the provided information is deemed insufficient for risk assessment, risk management organizations shall be requested to provide additional documents.

Furthermore, in principle, to secure adequacy of risk assessments, documents shall be based on the outcome of studies conducted at test facilities etc., that comply with Good Laboratory Practice (GLP), which shall also be compiled as a report by internationally recognized assessment organizations both domestic and abroad that comply with various guidelines effective in Japan or laid down by the Organization for Economic Co-operation and Development (OECD).

In addition, published literatures referenced in risk assessments must be considered fit for use by the Expert Committee on Fertilizers and Feeds of the FSCJ.

2. Assessment Using Limited Documents
For substances that are extremely unlikely to pose adverse effects on human health via ingestion of livestock or cultured fishery products (nutrients of substances classified as Exempt Substances including amino acids, vitamins, minerals, etc., or enzymes and viable bacterial preparations, etc.,) limited reference documents can be used for assessment when reasonable, depending on the level of existing scientific knowledge, including characteristics concerning toxicity, persistence, previous evaluations by international organizations etc., or when the substances are biological components, etc.

However, upon using limited documents for assessment, the rationale for doing so shall be described in the assessment report.

**Article 5: Re-evaluation of Risk Assessments**

The evaluation of the adverse effects in the previous assessment shall be reviewed appropriately, whenever it is found necessary as the results of a newly conducted toxicity study. In such cases of re-evaluation, up-to-date international evaluation standards and others shall be considered.

**Article 6: Revision of this Set of Guidelines**

To keep abreast of the latest trends concerning international risk assessments or advances in science, this set of Guidelines shall be revised as necessary.

**Chapter 2. Detailed Exposition**

**Article 1: Risk Assessment Under Item (i)**

1. Policy on Risk Assessment Under Item (i)
Risk Assessment Under Item (i) involves a comprehensive analysis to investigate the toxicological characteristics of components subject to risk assessment by reviewing existing knowledge on

biodisposition, i.e., pharmacokinetics (absorption, distribution, metabolism, and excretion), the persistence of components and findings observed in each toxicity study.

2. Outline of Components Subject to Risk Assessment
Properties, use methods and other characteristics of components subject to risk assessment shall be identified. For assessment, it is required to use documents containing outline information of the component including use (function), common name, chemical name, element symbol or molecular formula, atomic or molecular weight, chemical structure, properties, purpose, method and status of use (see Appendix 1).

3. Findings on Safety
Toxicological properties of components under assessment shall be identified. Documents containing biodisposition (pharmacokinetics), persistence, genotoxicity, acute toxicity, subacute toxicity, chronic toxicity, carcinogenicity, reproductive and developmental toxicity, microbiological acceptable daily intake (hereinafter referred to as "ADI") (in the case of antimicrobial substances) and other safety information are required for assessment (see Appendix 1).

- Biodisposition (pharmacokinetic) studies mainly involve extrapolating laboratory animal data including rodent data to humans. As for biodisposition (pharmacokinetic) studies in livestock, etc., persistence of the component under assessment and ingestion by humans (parent compounds and their metabolites) are investigated in addition to conducting residual analyses.

- Upon evaluating genotoxicity study results among various toxicity studies, it should be noted that if concerns over potential human genotoxicity cannot be excluded for components under assessment via ingestion of food, toxicological thresholds cannot be established for said component under assessment.

- In principle, toxicity studies excluding genotoxicity studies shall identify whether the highest doses are doses at which toxic effects are observed, and the lowest doses are doses at which toxic effects are absent, and whether each dose level is appropriately set so that dose-response relationships can be observed. In addition to this, presence or absence of toxic effects for each dose are also identified, and the toxicity observed for the lowest-observed-adverse-effect level (hereinafter referred to as "LOAEL") which is used as the basis for establishing the no-observed-adverse-effect level (hereinafter referred to as "NOAEL") shall be used as endpoint (toxicity index.)

- Policies on individual toxicity studies, etc., shall be determined by the Expert Committee on Fertilizers and Feeds of the FSCJ.

- In determining endpoints, findings in each toxicity study should be interpreted with sufficient rationale and from a scientific viewpoint with regard to statistical significance and dose correlation for each study, taking into account interspecies variability, dosage, duration of treatment, biodisposition (pharmacokinetics), etc., across studies. In doing so, the modes of toxic action should be elaborated to the extent possible.

4. Risk Assessment
Depending on the use, characteristics, etc., of the Feed Additives, the following approaches 1) through 3) shall be considered to determine whether it is necessary to establish ADIs and how to establish them when considered necessary, to determine whether it is possible to elucidate that the residual components of the Feed Additive would not pose adverse effects on human health under conditions of their intended use.
Furthermore, in principle, it is inappropriate to establish ADIs if concerns over *in vivo* genotoxicity of the components in question cannot be excluded, and if the latent genotoxicity may have a role in carcinogenesis.

1) Establishing ADIs
ADIs shall be established based on the following:

(1) Toxicological ADI
If as a result of conducting a comprehensive assessment on toxicity test to consider toxicological effects of a component on humans via ingestion of food derived from domestic animals, etc., multiple NOAELs are available for establishing an ADI, the minimum NOAEL value shall be adopted in principle after comparison of dose settings and animal species across studies.

However, if a NOAEL obtained from a particular study is more appropriate to use compared to NOAELs from other studies based on study design (duration, dose setting, etc.) and if the results from the study are fit to extrapolate to humans by comparison, the NOAEL from such study should be adopted as the basis for establishing an ADI.

If an appropriate NOAEL is not derived, the LOAEL can be used instead as a basis after due deliberation.

The toxicological ADI shall be established by specifying a NOAEL etc. selected by the above criteria and dividing it by the safety factor described in (4) below.

(2) Microbiological ADI
When components under assessment are antimicrobial components, microbiological ADIs shall be established based on minimum inhibitory concentrations (MICs) to consider their effects on the human gut microbiome when ingested via livestock or cultured fishery products.

(3) Establishing ADIs
When components under assessment are not antimicrobial substances, the toxicological ADIs shall be adopted as ADIs. If components under assessment are antimicrobial substances, the smaller value between the toxicological ADI and microbiological ADI shall be adopted.

(4) Safety Factor
A safety factor of 100 is set to take interspecies and inter-individual variabilities into account. It should be noted, however, that this safety factor of 100 is not an invariant and should be adjusted according to toxicity characteristics, test results, etc., as follows:

a) When using results from human studies, it is unnecessary to consider interspecies variability, and instead an appropriate safety factor[2] should be established based on the number of populations studied, etc., while taking inter-individual variability into account.
b) When establishing an ADI based on a LOAEL value instead of a NOAEL value, an additional safety factor of 1to10 is applied. Alternatively, the benchmark dose (BMD) method may be adopted.
c) Additional safety factors of 1to10 shall be applied depending on the validity of data used (availability of long-term toxicity studies, sufficiency of data from each toxicity study, etc.) and the severity of toxicological findings, etc.

2) Cases in Which Establishment of ADIs are Unnecessary
For substances that are considered to have minimal toxicity or have low persistence due to rapid metabolism and excretion etc., establishment of ADIs may be considered unnecessary, provided that clear rationales are submitted, even when ADIs are specifiable based on characteristics of toxicity or persistence of the components subject to assessment.

[2] A safety factor of 1 to 10 is adopted considering individual variability but with some exceptions.

3) Group ADI
If a component under assessment is considered to share common toxicological effects on humans with other substances upon comprehensive evaluation of structural similarities and outcome of biodisposition (pharmacokinetics), residue analyses and toxicity tests, and if the cumulative intake of these groups of substances are intended to be controlled as a whole, a group ADI encompassing these multiple substances shall be established by further evaluating results from various studies and methods of use, etc.

4) Assessment of Exempt Substances
For Exempt Substances, ADI shall be specified as necessary depending on knowledge regarding the component subject to assessment, including properties, its use as Feed Additive, persistence, exposure to humans, toxicity, etc., based on which evaluation will be made as to whether the residual Exempt Substances may potentially cause adverse effects on human health under its intended use as Feed Additives.

5. Assessment of Components for which Provisional Standards are Established
Risk assessments shall be conducted in accordance with "Procedure for Risk Assessment of Agricultural Chemicals for which Provisional Standards are Established" (FSCJ decision dated June 29, 2006).

**Article 2: Risk Assessment Under Item (v)**

1. Policy on Risk Assessment Under Item (v)
Potential adverse effects of Formulations on human health via food ingestion are evaluated in Risk Assessment Under Item (v) on the premise that the Formulation of which the assessment request was made would be used appropriately under intended use based on the following criteria: (1) Characteristics of the Formulation (safety of Technical Grade Active Ingredients and Excipients, etc.,) (2) Persistence of the Formulation when used in livestock, etc., and (3) Safety of the Formulation when used in livestock, etc. (see Appendix 2 of this set of Guidelines).

2. Information of Feed Additives
Basic information required for the assessment of Feed Additives shall be summarized.
Upon assessment, application documents, etc. to be submitted for the designation of Feed Additives, etc. shall contain information regarding the active substances of the Formulations to be assessed (Technical Grade Active Ingredients, Formulation, use/purpose, Feeds to which the Formulations will be added, and the added volume, history of development, etc.) under Article 2, paragraph (3) of the Feed Safety Act (Notification No. 54-Chiku-A-5002, February 4, 1980) (see Appendix 2 of this set of Guidelines.)

3. Knowledge of Human Safety
For Technical Grade Active Ingredients, results from Risk Assessment Under Item (i) should be used if available. If unavailable, evaluations shall be based on various toxicity test results.

Assessment policies for components of Technical Grade Active Ingredients that are non-active ingredients and Excipients, etc., shall correspond with the Guidance for assessment of additives to vaccines as veterinary medicinal products (Decision of the FSCJ dated October 14, 2014.)

The FSCJ stated in its "Regarding Risk Assessment" (Notification No. 342-Fusyoku, April 5, 2012) in response to a request for deliberation by the Ministry of Agriculture, Forestry and Fisheries that with respect to the amendments concerning substances among Excipients and diluents excluding calcium lignosulfonate and sodium lignosulfonate prescribed in paragraph 3, item (vi) of the Appended Table 2 of the Ministerial Ordinance on the Specifications and Standards of Feeds and Feed Additives (Ordinance of the Ministry of Agriculture, Forestry and Fisheries No. 35 of 1976),

the degree of adverse effects on human health of said substances are clear and fall under Article 11, paragraph 1, item (ii) of the Act[3], which should be noted.

Documents required for assessment shall include information on the Technical Grade Active Ingredient, information on substances contained in the Formulation, and information on persistence, etc., and if necessary, documents including information on various toxicity studies (see Appendix 2 of this set of Guidelines.)

4. Knowledge of Persistence
In principle, the persistence of the active ingredient should be examined using documents related to residue analyses using the Formulation.

5. Knowledge Concerning Safety for Livestock, etc.
Knowledge on safety for livestock etc. should be summarized as reference material for risk assessments evaluating the health effects on humans via ingestion of food derived from livestock etc. to which the Formulations were administered.

Required information for this purpose shall incorporate information such as outcomes from tolerance studies, feeding tests, and other tests on livestock, etc.

6. Risk Assessments
Regarding the assessment of Formulations, information on Feed Additives, knowledge on safety in humans, persistence, and safety in livestock, etc. are consolidated to evaluate the potential adverse effects of Feed Additives on human health through food under their intended use.

[3] Of the Excipients and diluents prescribed in paragraph 3 (vi) of Appended Table 2 of the Ministerial Ordinance on the Specification and Standards of Feeds and Feed Additives, separate risk assessments were conducted for calcium lignosulfonate and sodium lignosulfonate in accordance with Article 11, paragraph (1) of the Act in consideration of their properties.

**Appendix 1. Documents Required for Risk Assessment Under Item (i)**

| Information | | New | Revisions [a] |
|---|---|---|---|
| I | Outline of component subject to assessment | | |
| | 1. Use (function) | | |
| | 2. Common name | | |
| | 3. Chemical name | | |
| | 4. Element symbol or molecular formula | | |
| | 5. Atomic weight or molecular weight | | |
| | 6. Chemical structure | | |
| | 7. Information on properties, etc. | | |
| | 8. Purpose, method, and status of use (or history of development) | | |
| II | Existing knowledge regarding safety | | |
| | 1. Biodisposition (pharmacokinetics) study | | |
| | 2. Residue analyses | | |
| | 3. Genotoxicity study | | |
| | 4. Acute toxicity study | | |
| | 5. Subacute toxicity study | | |
| | 6. Chronic toxicity and carcinogenicity study | | |
| | 7. Reproductive and developmental toxicity study | | |
| | 8. Studies relevant to specification of microbiological ADI | | |
| | 9. Existing knowledge regarding effects on humans | | |
| | 1) Findings in humans [b] | | |
| | 2) Evaluations by international organizations, etc. | | |

: Necessary documents to be attached as a general rule upon request for assessment (reasons should be stated when certain documents are unavailable or omitted)

: Documents to be attached as necessary, e.g. when there are new findings

a: Cases in which assessment results already exist.

b: Existing knowledge regarding use outside of Feed such as Feed Additive etc., e.g., accidental human ingestions, estimated daily intake, etc.

**Appendix 2. Documents Required for Risk Assessment Under Item (v)**

| Information | | New | Revisions [a] |
|---|---|---|---|
| I | Outline of Formulation subject to assessment | | |
| | 1. Information on Technical Grade Active Ingredient | | |
| | 2. Information on Formulation (method of preparation and Excipients, etc.) | | |
| | 3. Use (function) | | |
| | 4. Information on Feed to which the Formulation is added to and volume of addition | | |
| | 5. History of development (or purpose and status of use) | | |
| II | Information concerning safety | | |
| | 1. Information regarding safety of Technical Grade Active Ingredient [bc] | | |
| | 1) Biodisposition (pharmacokinetics) study | | |
| | 2) Genotoxicity study | | |
| | 3) Acute toxicity study | | |
| | 4) Subacute toxicity study | | |
| | 5) Chronic toxicity and carcinogenicity study | | |
| | 6) Reproductive and developmental toxicity study | | |
| | 2. Residue analysis | | |
| | 3. Safety study on livestock, etc. | | |
| | 4. Safety information regarding Excipients, etc. | | |
| | 5. Documents on microbiological ADI [d] | | |
| | 6. Documents on antimicrobial-resistant bacteria | | |

: Necessary documents to be attached as a general rule upon request for assessment (reasons should be stated when certain documents are unavailable or omitted)

: Documents to be attached as necessary, e.g. when there are new findings

a: Cases in which assessment results already exist.

b: If the component undergoes Risk Assessment Under Item (i), results from the assessment should be referred to in principle.

c: Testing on Formulations are permitted as long as it is feasible to confirm the safety of the Technical Grade Active Ingredients.

d: In principle, in the case of antimicrobial substances. When components are considered to have antimicrobial properties, additional documents may be required.

**(Revision history)** April 2024: “Minister of Health, Labour and Welfare" replaced by “Prime Minister” in the “Exempt Substance” entry of “Definitions.”