Provisional translation

Decision of May 2019

Revised in April 2024

Expert Committee on Apparatus and containers/packages

Food Safety Commission of Japan

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Guidelines for the Risk Assessment of Food Apparatus, Containers, and Packaging

May 2019
(Revised in April 2024)

Food Safety Commission of Japan (FSCJ)

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Chapter 1: General Provisions

Article 1: Background

The Food Safety Commission of Japan (FSCJ) has established guidelines for the assessment of the effect of food on health (hereinafter referred to as "the risk assessment"), based on "Basic Matters in Article 21 paragraph (1) of the Food Safety Basic Act[1]" (the Cabinet Decision, January 16, 2004) in consideration of fairness and transparency in risk assessment.

Regarding food apparatus, containers, and packaging (ACP), the FSCJ has conducted the risk assessments related to amendment of standards and criteria under the Food Sanitation Act (Act No. 233, 1947) as necessary, based on requests from the Ministry of Health, Labour and Welfare (MHLW). Under the negative list system of the Food Sanitation Act, the use of substances has been restricted only when some standards and criteria were established on those substances. However, the FSCJ expects to conduct risk assessment based on requests from the MHLW continuously, with the recent amendment of the Food Sanitation Act (promulgation, June 13, 2018) and the introduction of a positive list system. Under the positive list system, the use of substances is principally prohibited except where some standards and criteria have been established, based on results of assessment on the substances.

In this environment -- where the importance of enhancing fairness and transparency in risk assessment and clarifying the data required for risk assessment are increasing -- the FSCJ has established the "Guidelines for the Risk Assessment of Food Apparatus, Containers, and Packaging", which considers approaches for risk assessments overseas and the situation related to risk assessment in Japan.

Article 2: Purpose

The Guidelines are intended to define the policies and methods of the risk assessment and scope of information and data required to assess human health effects of raw materials used for ACP, for the purposes of further enhancing fairness and transparency in assessments and facilitating deliberations.

Article 3: Definitions

①General definitions

○ Apparatus, containers and packaging

The term refers to "apparatus" prescribed in Article 4, paragraph (4) of the Food Sanitation Act and "containers and packaging" prescribed in Article 4, paragraph (5) of the said Act that are specifically provided as follows.

(1) Apparatus

Tableware, kitchen utensils, and other machines, implements, and other articles which are used for collecting, producing, processing, cooking, storing, transporting, displaying, delivering, or consuming food or additives and which come into direct contact with food or additives.

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[1] It is noted in Article 1, paragraph 3, item (1). 3 of the said Act that "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") to clearly define data required for assessment, and to revise it if necessary.

(2) Containers and packaging
Articles that contain or wrap food or additives and are offered “as is” when delivering food or additives.

○ Assessment-Requested Substance
Substances (excluding substances generated by chemical change of such substances) that are contained as raw material in the materials that are specified for the Order for Enforcement of the Food Sanitation Act (the Cabinet Order) by considering the impact on public health of eluting or seeping out the ingredients into food, prescribed in Article 18, paragraph (3), the Food Sanitation Act. Risk management organizations request the FSCJ for assessment of those substances, referred to as an “Assessment-Requested Substance,” based on Article 24 paragraph (1), item (1) of the Food Safety Basic Act (Act No. 48 of May 23, 2003).

②Migration testing
○ Dietary Concentration (DC)
Concentration of the subject substance in a daily unit of meal. It is estimated by converting the concentration of the subject substance in food simulant obtained from migration testing or other appropriate way, by Distribution Factor, Consumption Factor and, as necessary, Reduction Factor.

○ Food simulant
Solution simulating physical and chemical properties of food in each food category (see Table 2 in Appendix 2 for details).

○ Food category
Categories of foods classified according to their physical and chemical properties (see Table 2 in Appendix 2 for details).

○ Distribution Factor (DF)
A factor to indicate the ratio of ACP used for foods in specific food categories in specific type of materials. The ratio is calculated based on the usage status of materials for manufacturing ACP (see Table 5 in Appendix 2 for details).

○ Consumption Factor (CF)
A factor to indicate the ratio of amount of meal that makes contact with specific type of materials. The ratio is calculated based on the usage status of materials for manufacturing ACP (see Table 5 in Appendix 2 for details).

○ Reduction Factor (RF)
A factor used for lowering a value of predefined Consumption Factor or Distribution Factor, from the view point of reflecting actual usage status more accurately when restricting the scope of application of Assessment-Requested Substance.

③Toxicology
○ Genotoxic substance
A substance or its metabolites suspected to directly affect DNA, inducing gene mutation or chromosomal aberration as a result.

○ Genotoxic carcinogen

A substance or its metabolites suspected to directly affect DNA, inducing gene mutation or chromosomal aberration as a result, which is considered to be a part of a mechanism of carcinogenesis.

Article 4: Approach for the risk assessment of ACP

1. Scope

The Guidelines shall be applied to the following types of materials and substances used in ACP.

(1) Subject materials
Synthetic resin

(2) Subject substances
Substances that migrate into foods, due to contact of the foods with ACP, either from the layer that directly contacts the foods (direct-food-contact layer) or from the layer that does not directly contact the foods (indirect-food-contact layer). These substances include intentionally used substances as raw materials for materials of ACP, and non-intentionally contained substances in materials of ACP (such as impurities, byproducts, and decomposition products).

2. Procedures of assessment

These Guidelines describe the procedures of assessment that principally takes a tiered approach, using results of various toxicity tests and related studies or other relevant information required for assessment according to the Tier of Dietary Concentration (Tier of DC) of the subject substance in principle. Actual assessment will be conducted by the following procedures.

(1) Decide a Tier of DC the subject substance falls under, based on the Dietary Concentration of the subject substance calculated from migration testing results (see “3. Decision of Tier of Dietary Concentration (Tier of DC)” for details).
(2) Assess toxicity of the subject substance based on the results of various toxicity tests and related studies or other relevant information required for each Tier of DC (see “4. Toxicity assessment” for details).
(3) Assess the exposure level of the subject substance in human population of interest (see “5. Assessment of exposure level” for details).
(4) Determine the risk from ingestion of the subject substance based on the results of assessments of the toxicity and exposure level of the substance (see “6. Risk characterization” for details).

3. Decision of Tier of Dietary Concentration (Tier of DC)

(1) Outline
The degree of migration of subject substances shall be assessed based on the results of migration testing using food simulants and test samples of subject materials containing subject substances. Tier of DC of the subject substance (see Table 1. for details) shall be decided by converting the concentration of the subject substance in the food simulant to relevant Dietary Concentration, in accordance with the description in Article 2 of Chapter 2.

Table 1. Tier of DC and Concentration Range

Concentration range		Tier of DC
	0.5 μg/kg or less	Tier I
More than 0.5 μg/kg and	0.05 mg/kg or less	Tier II
More than 0.05 mg/kg and	1 mg/kg or less	Tier III
More than 1 mg/kg		Tier IV

(Note) Description of Tier of DC

○ Tier I

For the subject substance which has no-genotoxic concern, lifetime carcinogenic risk of that substance in this tier is estimated to be 10^{-6} or less[2], even if that substance is a carcinogen. If the subject substance in this tier can be considered to have no genotoxicity relevant to living organisms, that substance is generally supposed to have lower concerns over non-carcinogenic toxicity and non-genotoxic carcinogenicity than the subject substance in Tier II.

○ Tier II

Dietary Concentration of the subject substance in this tier is equal to or less than the value of TTC (Threshold of Toxicological Concern[3]) of Class III of Cramer structural classification by Munro (1996)[4]. If the subject substance in this tier can be considered to have no genotoxicity relevant to living organisms, that substance is generally supposed to have low concerns over non-carcinogenic toxicity and non-genotoxic carcinogenicity.

○ Tier III or Tier IV

For the subject substance in this tier, concerns over non-carcinogenic toxicity and non-genotoxic carcinogenicity are not supposed to be low in advance. From the view point of exposure level, the subject substance in Tier III is supposed to have lower concern than the subject substance in Tier IV.

(2) Basic requirements for migration testing and analysis

In principle, assessment shall be conducted based on the results of migration testing and analytical results each of which fulfill the following.

① Results of migration testing and analytical results performed by test laboratories capable of conducting them appropriately.

② Analytical results obtained by methods of analysis with validated or verified good

[2] A risk level of a substance resulting adverse effects that is as low as a level of a risk that one seldom encounters in normal life, even if that substance is continuously ingested through human lifetime.

[3] TTC (Threshold of Toxicological Concern) approach is used for screening and prioritization of chemical substances in safety assessment when human exposure can be estimated with insufficient hazard data.

[4] Munro IC, Ford RA, Kennepohl E and Sprenger JG: Correlation of a structural class with No-Observed-Effect-Levels: a proposal for establishing a threshold of concern. *Food Chem. Toxicol*., 1996; 34: 829-867.

performance.

4. Toxicity assessment

(1) Outline

Assess toxicity of the subject substance based on the results of various toxicity tests and related studies or other relevant information required for each Tier of DC, and set Health-Based Guidance Value (HBGV) (e.g.e.g., ADI/TDI) as necessary (see Article 3 of Chapter 2, for details of various toxicity tests and related studies or other relevant information required for each Tier of DC and the methods of these tests and studies).

(2) Basic requirements for toxicity tests and related studies

In principle, assessment shall be conducted based on the results of toxicity tests and related studies that fulfill the following.

① Results of toxicity tests and related studies performed by test laboratories that were certified for proper management and operation (GLP-facilities).

② Results of toxicity tests and related studies performed according to the latest Guidelines established by the Organisation for Economic Co-operation and Development (OECD).

(3) Interpretation of results of toxicity tests and related studies

① Interpretation of the threshold of genotoxicity

Despite that the presence of threshold of genotoxicity has been a subject of international discussion, an agreement is not yet reached. Accordingly, risk assessment shall be conducted for the moment under the assumption that no such threshold is present in principle.

② Determination of point of departure (POD)

a. If the subject substance is considered to have threshold for a toxicity observed, NOAEL shall be determined in consideration of the following points in principle.
   (a) The maximum/minimum doses are set to the level at which toxic effects are observed/not-observed respectively.
   (b) Dose levels are set so as to provide a dose-response relationship[5].
b. If no toxic effects are observed even at the maximum dose, that maximum dose shall be taken as NOAEL. If toxic effects are observed even at the minimum dose, that minimum dose shall be taken as LOAEL.
c. When NOAEL cannot be determined, the benchmark dose approach can be used.

(4) Setting HBGV (ADI/TDI)

① Selection of NOAEL or other POD value for setting HBGV (ADI/TDI)

If different NOAELs or other POD values are determined as a result of comprehensive assessment of toxicity, these values shall be compared by animal species and by toxicity studies, then the minimum NOAEL or other POD value shall be selected for setting ADI and TDI in principle. For selecting NOAEL or other POD value, the following points shall be taken into consideration.

a. If a test method has more scientific validity in its design and results by far than others or takes a longer test period, more weight shall be placed on NOAEL or other POD

[5] Dose levels desirably shall be set with an appropriate adjustment so as to secure enough margin between NOAEL and the estimated human oral exposure level.

value that was determined based on the result of such test.

b. If data on toxicokinetics and toxicodynamics are available, more weight shall be placed on NOAEL or other POD value that was determined based on the test results obtained from animal species that was most similar to human in toxic effects.

② Uncertainty factor

At present, an uncertainty factor of 100 is basically used in consideration of interspecies difference and interindividual difference. However, an appropriate value of uncertainty factor shall be established with additional considerations in the following cases.

a. If data from human studies are used, interspecies difference is unnecessary to be considered. In this case, the uncertainty factor of a value from1 to 10 shall be used considering interindividual differences depend on the size of a target group, among other factors.
b. If subchronic toxicity data from 90-day oral toxicity studies are used, the uncertainty factor is multiplied by an additional uncertainty factor from 1 to 10 considering the limited study period.
c. In the following cases, use of an additional factor from 1 to 10 for each case shall be considered for multiplying the uncertainty factor: 1) If sufficient information is unavailable, 2) If the subject substance shows serious toxicity[6], 3) If ADI/TDI is set based on LOAEL, and so on.
d. If sufficient data on toxicokinetics or toxicodynamics with scientific validity on the subject substance are available, such data shall be used for determining an uncertainty factor for interspecies difference or interindividual difference.

③ Setting group ADI/TDI

With regard to a group of subject substances that fall within a same degree of toxicity and may cause additively physiological and/or toxic effects, ADI/TDI shall be set as that of structures from the viewpoint of management of cumulative intake.

In principle, a group ADI/TDI shall be set based on the lowest value of NOAELs or other POD values among that of subject substances in the group. The lowest value of NOAELs or other POD values shall be selected considering also the following.

a. A greater weight shall be placed on NOAEL or other POD value with higher reliability in terms of scientific validity of test design or results and a length of test period.
b. If NOAEL or other POD value of a particular subject substance in a group is remarkably different from that of other substances in the group, that substance shall be excluded from the group and ADI/TDI for it shall be set separately.

④ A case where no ADI/TDI need be set

For the subject substance whose toxicity is judged to be extremely low, it may be considered that no ADI/TDI need be set by providing explicit evidences based on information such as toxicological characteristics, even if ADI/TDI for the substances can be set.

5. Exposure assessment

(1) Outline

In principle, daily dietary exposure to the subject substance (per body weight) shall be estimated by Dietary Concentration of the substance, dietary intake, and body weight of a

[6] Serious toxicity includes carcinogenicity, teratogenicity, etc.

target human population. In estimating dietary exposure, considerations shall be necessary for preventing underestimation.

(2) Exposure scenario

① Dietary Concentration of the subject substance

In principle, Dietary Concentration of the subject substance shall be obtained by calculation from the concentration in food simulant based on migration testing result. (For calculation of Dietary Concentration, see "Appendix 2. Method of Migration testing and calculation method of Dietary Concentration")

② Body weight and dietary intake of a target human population

a. For estimating dietary exposure, body weight shall be the average body weight of Japan's population based on the latest decision of the FSCJ. Dietary intake shall be the average total intake from all food groups of Japan's population provided by the National Health and Nutrition Survey conducted by the MHLW.

b. A human population that is supposed to be highly exposed or sensitive to the subject substance shall also be targeted as necessary in consideration of the usage of ACP containing the substance, and of the toxicity tests results of the substance. For estimating dietary exposure, body weight shall be the average body weight of relevant population based on the latest decision of the FSCJ. Dietary intake shall be the average total intake from all food groups of relevant population provided by the National Health and Nutrition Survey conducted by the MHLW. If the above information is unavailable, the body weight and dietary intake of relevant population shall be estimated appropriately from other available information.

6. Risk characterization

(1) Outline

If Dietary Concentration of the subject substance falls under "Tier I" or "Tier II", risk characterization shall be conducted based on available information on genotoxicity and results of genotoxicity tests in principle.

If it falls under "Tier III" or "Tier IV", the degree of health risk from intake of the subject substance for the target human population shall be estimated by comparing the estimated daily dietary exposure of the subject substance with HBGV (ADI/TDI) or POD value (e.g.e.g., NOAEL) of the substance.

(2) Principal stance for risk characterization

① When Dietary Concentration falls under "Tier I" or "Tier II"

a. Subject substances assessed to be genotoxic substances

(a) For intentionally used substances as raw materials for materials of ACP, the use should not be permitted in principle.

(b) For non-intentionally contained substances in materials of ACP (such as impurities, byproducts and decomposition products), the need for restriction of use of raw materials that causes those inclusions shall be determined comprehensively based on relevant information and knowledge on the substances[7].

[7] Relevant information and knowledge include, for example, information on ACP, migration testing results, information on physical and chemical properties for the substance, and TTC (0.15 μg/person/day: 0.05 μg/kg as DC) at which the lifetime carcinogenic risk is estimated to be 10^{-6}. This TTC is set in the "Review of the TTC approach and development of new TTC decision tree (WHO & EFSA (2016))" for the substances that have chemical structural alerts for the potential

b. Subject substances not assessed to be genotoxic substances
If Dietary Concentration of the subject substance is below the upper limit of "Tier I" or "Tier II", the health risk from the substance shall be presumed to below enough in general, since the substance is supposed to have low concerns over non-carcinogenic toxicity and non-genotoxic carcinogenicity.

② When Dietary Concentration falls under "Tier III"

a. Subject substances assessed to be genotoxic substances
The health risk from the subject substance shall be determined with the same stance as that for the substance of "Tier I" or "Tier II".

b. Subject substances not assessed to be genotoxic substances

(a) When HBGV (ADI/TDI) is set
If estimated daily dietary exposure of the subject substance is equal to or lower than ADI/TDI, the health risk from the substance is presumed to be low enough in general. If estimated daily dietary exposure exceeds ADI/TDI, conditions where the restriction of use of raw materials is required shall be considered since the health risk from the substance cannot be determined to be sufficiently low in general.

(b) When no HBGV (ADI/TDI) need to be set
The health risk shall be determined based on the level of margin of exposure (MOE) calculating it from NOAEL or other POD value and the estimated daily dietary exposure of the subject substance. In that case, the risk shall be comprehensively determined in consideration of the grounds for judging ADI/TDI to be unnecessary and the estimated daily dietary exposure. When NOAEL or other POD value is obtained from subchronic toxicity test, if the value of MOE of the subject substance is approximately between 100 and 1,000 or more, the health risk from the substance is determined to be sufficiently low in general.

③ When Dietary Concentration falls under "Tier IV"

a. Subject substances assessed to be genotoxic carcinogens

(a) For intentionally used substances as raw materials for materials of ACP, the use should not be permitted in principle.

(b) For non-intentionally contained substances in materials of ACP (such as impurities, by-products and decomposition products), the health risk from the substance shall be comprehensively determined based on the MOE approach. If the MOE of the subject substance is approximately 10,000 or more, the health risk from the substance is determined to be sufficiently low in general. If the MOE of the subject substance is insufficient, conditions where the restriction of use of raw materials is required shall be considered since the health risk from the substance cannot be determined to be sufficiently low in general.

b. Subject substances not assessed to be genotoxic carcinogens

(a) When HBGV (ADI/TDI) is set
The health risk from the subject substance shall be determined with the same stance as that for the substance of "Tier III".

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genotoxic carcinogenicity or the substances determined to have genotoxicity by the results of genotoxicity tests such as Ames test.

(b) When no HBGV (ADI/TDI) need to be set
The health risk shall be determined based on the level of MOE calculating it from NOAEL or other POD value and the estimated daily dietary exposure of the subject substance. In that case, the risk shall be comprehensively determined in consideration of the grounds for judging ADI/TDI to be unnecessary and the estimated daily dietary exposure. When NOAEL or other POD value is obtained from various toxicity tests, if the value of MOE of the subject substance is approximately 100 or more, the health risk from the substance is determined to be sufficiently low in general.

Article 5: Approach for the documents required

1. In principle, the appropriate documents provided by risk management agencies should be used for the risk assessment. If the provided information is insufficient for the risk assessment, the risk management organization shall be requested to provide the additional documents as necessary.
2. The scope of documents required for the risk assessment is prescribed in Appendix 1.

Article 6: Reassessment

If there arises a need to revise judgement in the previous assessment in consideration of the latest scientific findings and the international trends of assessment standards, the previous assessment shall be reviewed appropriately.

Article 7: Revision of the Guidelines

When the Expert Committee on ACP adopts a new approach for migration testing or toxicity tests in response to the up-to-date international trends of the risk assessment, trends of domestic regulation on ACP, and advances in science, the guideline shall be revised as necessary.

Chapter 2: Detailed Exposition

Article 1: Chemistry information for the Assessment-Requested Substance

The FSCJ requests to provide information on the Assessment-Requested Substance listed in Table 2.

For non-intentionally contained substances in materials of ACP (such as impurities, by-products and decomposition products) that are estimated or identified according to item 1 of Article 2, the FSCJ requests to provide available information regarding item (1) and (2) of 1of Table 2.

The FSCJ may also request additional information if deemed necessary for assessment.

Table 2. Information items requested

Item	Note
1. **Identity**	
(1) **Name, structure, etc.**	・ If the Assessment-Requested Substance is a base polymer or a polymer used as an additive (hereinafter refer to as a polymeric additive), include the information on monomers forming the polymer. ・ If the Assessment-Requested Substance is a mixture of chemical substances, include information on individual substances as far as possible.
① **Substance name**	・ General name, conventional name, IUPAC name, etc. ・ Name of commercially available products if any.
② **CAS number**	・ If CAS number cannot be identified precisely, describe as such providing a reference CAS number if any.
③ **Chemical and structural formula**	
④ **Molecular weight**	・ If the Assessment-Requested Substance is a base polymer or a polymeric additive, include molecular weight of monomers forming the polymer, average molecular weight of the polymer (weight (Mw) and count (Mn)), distribution of molecular weight and a ratio of polymers with molecular weight of 1,000 or less.
⑤ **Spectrum data**	・ Spectrum data that allow identification of a substance by instrumental analyses (Fourier transform infrared spectroscopy (FTIR), ultraviolet spectroscopy (UV), nuclear magnetic resonance (NMR), mass spectrometry (MS), etc.)
⑥ **Composition**	※Only when the Assessment-Requested Substance is a mixture of chemical substances, a base polymer or a polymeric additive. ・ Composition ratio of chemical substances in the mixture or ratio of the monomers in the polymer.
(2) **Physical and chemical properties**	・ If the Assessment-Requested Substance is a base polymer or a polymeric additive, include the information on monomers forming the polymer. ・ If the Assessment-Requested Substance is a mixture

	of chemical substances, include information on individual substances as far as possible.
① **Boiling point**	・ Data from literature indicating the source are acceptable.
② **Melting point**	・ Data from literature indicating the source are acceptable.
③ **Glass transition temperature, Ball pressure temperature etc.**	※Only when the Assessment-Requested Substance is a base polymer. ・ Data from literature indicating the source are acceptable.
④ **Density and crystallinity**	※Only when the Assessment-Requested Substance is a base polymer. ・ Data from literature indicating the source are acceptable.
⑤ **Water absorption**	※Only when the Assessment-Requested Substance is a base polymer. ・ Data from literature indicating the source are acceptable.
⑥ **Octanol/water partition coefficient (log Pow)**	・ Values calculated *in silico* are acceptable
⑦ **Others**	・ Other physical and chemical properties (solubility, stability, reactivity, degradability, etc. of the substance under some physical and chemical conditions such as temperature, light, solvent, and so on.) ・ Data from literature indicating the source are acceptable.
(3) **Manufacture method etc.**	・ Reaction-starting material, solvent, catalyst, other raw materials (manufacturing aids, etc.), chemical equation, manufacturing processes, etc.
(4) **Other**	・ Other basic information (purity of general products, impurities (if the Assessment-Requested Substance is a base polymer or a polymeric additive, information of a residual monomer shall be included.) , etc.)
2. **Purpose and condition of use**	
(1) **Purpose of use**	・ Including information on intended technical effects.
(2) **Condition of use**	
① **Groups and types of synthetic resin**	・ Groups and types of synthetic resin in which the Assessment-Requested Substance is used.
② **Food category**	・ Food category handled with ACP that contain the Assessment-Requested Substance as a raw material (see Attached Table 2 of Appendix 2 for details of food categories).
③ **Temperature and time condition**	・ Condition of temperature and time under which foods contact with ACP that contain the Assessment-Requested Substance as a raw material.
④ **Other**	・ Information on other conditions of use (range of amount in material, etc.)

3. **Draft standards and criteria**	・ Draft proposal for specifying a scope of use (groups and types of synthetic resin, food category, temperature, time, etc.), and restriction of amount in material, etc.
4. **Status of use in Japan and overseas**	・ Information on usage status, scope of use, restrictions, and others.
(1) **Japan**	・ Current standards and criteria (including those for synthetic resins that are outside the scope of use of the Assessment-Requested Substance, if any).
(2) **EU**	
(3) **The United State**	
(4) **Other countries**	
5. **Assessments in overseas**	
6. **Others**	・ Other useful information for the risk assessment (references on migration of relevant substances into foods, status of use of relevant substances in any products other than ACP, and others).

Article 2. Findings on migration into foods

Findings on migration of the Assessment-Requested Substance into foods shall be provided according to this article. If the Assessment-Requested Substance is a polymeric additive, the findings shall be provided according to Article 4.

1. Migration testing and Dietary Concentration

The FSCJ requests to provide information on the condition and results of migration testing and calculation of Dietary Concentration (see Appendix 2 for details of migration testing methods and calculation method of Dietary Concentration).

2. Tier of DC

Tier of DC of the subject substance shall be decided by comparing the Dietary Concentration calculated based on the result from migration testing and the concentration range shown in Table 1.

Table 1. Tier of DC and the Concentration Range (re-shown)

Concentration range		Tier of DC
	0.5 μg/kg or less	Tier I
More than 0.5 μg/kg and	0.05 mg/kg or less	Tier II
More than 0.05 mg/kg and	1 mg/kg or less	Tier III
More than 1 mg/kg		Tier IV

Article 3: Findings on safety

Findings on safety of the Assessment-Requested Substance shall be provided according to this article. If the Assessment-Requested Substance is a polymeric additive, the findings shall be provided according to Article 4.

1. Outline of test items and information required for each Tier of DC

Test items required for each Tier of DC are basically described in (1) to (4) below. In addition,

regardless of Tier of DC, the FSCJ requests to collect and provide available information on the subject substance, particularly information on the toxicities that are not mandated to submit test results in each Tier.
If any of the requirements comes under the item described in "3. Toxic effects and substances requiring special attention", the FSCJ requests to submit relevant results of toxicity tests and related studies in addition. Moreover, the FSCJ may request additional results of toxicity tests and related studies, if the FSCJ deems it necessary for assessment.
If any sufficient information is available in terms of toxicity assessment of subject substances, the relevant information may be used for the assessment in place of results of toxicity tests and related studies.

(1) Dietary Concentration "Tier I"
Regarding the substance that falls under the Dietary Concentration "Tier I", it is mandatory to present consideration of genotoxicity based on available information[8]. If genotoxicity information is not available, the FSCJ requests the results of the genotoxicity test in principle.

(2) Dietary Concentration "Tier II"
Regarding the substance that falls under the Dietary Concentration "Tier II", it is mandatory to submit the results of the genotoxicity test (see "2 (1) Genotoxicity test" for details). Results of general toxicity tests are not mandatory.

(3) Dietary Concentration "Tier III"
Regarding the substance that falls under the Dietary Concentration "Tier III", the results of genotoxicity and subchronic toxicity test are mandatory (see "2 (1) and (2)" for details).

(4) Dietary Concentration "Tier IV"
Regarding the substance that falls under the Dietary Concentration "Tier IV", it is mandatory to submit the test results of genotoxicity, subchronic toxicity, reproductive toxicity, developmental toxicity, chronic toxicity, carcinogenicity test and ADME study (see "2 (1) and (2)" for details).

Reference Table 1. Outline of test items and information[*1] required for each Tier of DC

Tier of DC		Test item
Tier I	0.5 μg/kg or less	-[*2]
Tier II	More than 0.5 μg/kg and up to 0.05 mg/kg	Genotoxicity test
Tier III	More than 0.05 mg/kg and up to 1 mg/kg	Genotoxicity test Subchronic toxicity test
Tier IV	More than 1 mg/kg	Genotoxicity test Subchronic toxicity test

[8] Available information includes the reported results of genotoxicity tests, information on structural similarities with known genotoxic substances, and information related to structure-activity relationship. Genotoxicity test or other related tests may be conducted for supplementing the available information.

	Reproductive toxicity test Developmental toxicity test Chronic toxicity test Carcinogenicity test ADME study

*1: In addition to the test items listed in this table, regardless of Tier of DC, the FSCJ requests to collect and provide available information on the subject substance, particularly information on the toxicities that are not mandated to submit test results in each Tier.
*2: For the assessment of the substance of "Tier I", it is mandatory to present consideration of genotoxicity based on available information. If genotoxicity information is not available, the FSCJ requests the results of the genotoxicity test in principle.

2. Details of tests

(1) Genotoxicity test

① Dietary Concentration "Tier II"

a. Step 1

Results from two or more *in vitro* tests in combination of following (a) and (b) are requested in principle.

(a) Reverse mutation test with bacteria

(Example of the test method)

- OECD TG471 (Bacterial Reverse Mutation Test)

(b) Genotoxicity test using mammalian cells (one or more from following three tests are requested)

○ Chromosomal aberration test using mammalian cells

(Example of the test method)

- OECD TG473 (*In Vitro* Mammalian Chromosomal Aberration Test)

○ Micronucleus test using mammalian cells

(Example of the test method)

- OECD TG487 (*In Vitro* Mammalian Cell Micronucleus Test)

○ Gene mutation test with mammalian cells (mouse lymphoma TK assay)

(Example of the test method)

- OECD TG490 (*In Vitro* Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene)

b. Step 2

If genotoxicity of the subject substance is undeniable based on the results from tests designated in Step 1, additional results of following *in vivo* tests may be requested to assess *in vivo* genotoxicity.

(Example of *in vivo* test)

○ Micronucleus test using rodents

(Example of the test method)

- OECD TG474 (Mammalian Erythrocyte Micronucleus Test)

○ Mutation test using transgenic rodents
(Example of the test method)
- OECD TG488 (Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays)

② Dietary Concentration "Tier III" or "Tier IV"

a. Step 1

Results from two or more *in vitro* tests as described in ① a and results of rodent micronucleus test are requested, in principle.

b. Step 2

If genotoxicity of the subject substance is undeniable based on the results from tests designated in Step 1, results of additional tests may be requested to supplement the above test results. (For example, results of *in vivo* tests such as transgenic rodent mutation test may be requested if the result of bacterial reverse mutation test is positive.)

(2) Toxicity tests (except genotoxicity test)

The following ① through ⑥ are the toxicity tests or the related study that are required for assessment. As for a toxicity test, among those -- which is to be conducted with two animal species in principle -- it may be allowed to assess based on the test results using a single species only if the reason to use the test with a single species is well explained and is deemed reasonable.

① Subchronic toxicity test

Subchronic toxicity shall be tested for 90 days, using one species of rodent (usually rats) and one species of non-rodent (usually dogs) in principle.

(Example of the test method)
- OECD TG408 (Repeated Dose 90-day Oral Toxicity Study in Rodents)
- OECD TG409 (Repeated Dose 90-day Oral Toxicity Study in Non-Rodents)

② Reproductive toxicity test

This test shall be conducted using one species of rodent (usually rats) in principle.

(Example of the test method)
- OECD TG416 (Two-Generation Reproduction Toxicity Study)
- OECD TG443 (Extended One-Generation Reproductive Toxicity Study)

③ Developmental toxicity test

This test shall be conducted using one species of rodent (usually rats) and one species of non-rodent (usually rabbits) in principle.
If teratogenicity is observed in rodents, one of the two species of animals used in this test, and if NOAEL or other POD value for the teratogenicity does not give basis for setting ADI/TDI, an assessment based on the test results using one species of rodent only is acceptable.

(Example of the test method)
- OECD TG414 (Prenatal Developmental Toxicity Study)

④ Chronic toxicity test

This test shall be conducted using one species of rodent (usually rats) in principle.
If the case falls under "(2) of 2" of "Handling of one-year repeated dose oral toxicity study in dogs for the risk assessment of agricultural chemicals (decision of Pesticides Expert Committee on December 21, 2017)", results of test conducted using one species of non-rodent (dogs) shall also be requested.

(Example of the test method)
- OECD TG452 (Chronic Toxicity Studies)
- OECD TG453 (Combined Chronic Toxicity/Carcinogenicity Studies)

⑤ Carcinogenicity test

This test shall be conducted using two species of rodent (usually rats and mice) in principle.
If a combined chronic toxicity/carcinogenicity test was conducted as a chronic toxicity test in one species of rodent, the assessment may be conducted based on the results from that test and results from carcinogenicity test using one species of rodent (which should not overlap with that used in the combined chronic toxicity/carcinogenicity test).

(Example of the test method)
- OECD TG451 (Carcinogenicity Studies)

⑥ ADME study

ADME study shall be conducted using one species of rodent (usually rats) in principle. If target organs and degree of toxic signs are considerably different between rodents and non-rodents, it is advisable to conduct the assessment using an additional species of non-rodent in view of extrapolation to humans.

(Example of the test method)
- OECD TG417 (Toxicokinetics)

Reference Table 2. Details of toxicity tests (except genotoxicity test)

Test items	Animal species to be used in principle[*1]	Example test methods
Subchronic toxicity test	One rodent (usually rats) and one non-rodent (usually dogs)	OECD TG408 OECD TG409
Reproductive toxicity test	One rodent (usually rats)	OECD TG416 OECD TG443
Developmental toxicity test	One rodent (usually rats) and one non-rodent (usually rabbits)[*2]	OECD TG414
Chronic toxicity test	One rodent (usually rats)[*3]	OECD TG452 OECD TG453
Carcinogenicity test	Two rodent (usually rats and mice)[*4]	OECD TG451
ADME study	One rodent (usually rats)[*5]	OECD TG417

*1: For a toxicity test that is to be conducted with two animal species in principle, it may be

allowed to assess based on the test results using a single species if the reason to use the test with a single species is well explained and deemed reasonable.

*2: If teratogenicity is observed in rodents, one of the two species of animals used in this test, and if NOAEL or other POD value for the teratogenicity does not give basis for setting ADI/TDI, an assessment based on the test results using one species of rodent only is acceptable.

*3: If the case falls under " (2) of 2" of "Handling of one-year repeated dose oral toxicity study in dogs for the risk assessment of agricultural chemicals (decision of Pesticides Expert Committee on December 21, 2017) ", results of test conducted using one species of non-rodent (dogs) shall also be requested.

*4: If a combined chronic toxicity/carcinogenicity test was conducted as a chronic toxicity test in one species of rodent, the assessment may be conducted based on the results from that test and results from carcinogenicity test using one species of rodent (which should not overlap with that used in the combined chronic toxicity/carcinogenicity test).

*5: If target organs and degree of toxic signs are considerably different between rodents and non-rodents, it is advisable to conduct the assessment using an additional species of non-rodent in view of extrapolation to humans.

3. Toxic effects and substances that require special attention

(1) Toxic effects that require special attention

① Neurotoxicity

No toxicity tests specialized to neurotoxicity shall be required regardless of Tier of DC of the subject substance. However, if neurotoxicity is suspected from available information[9], test results that provide information on neurotoxicity may be required regardless of the Tier of DC.

② Immunotoxicity

No toxicity tests specialized to immunotoxicity shall be required regardless of Tier of DC of the subject substance. However, if immunotoxicity is suspected from available information, test results that provide information on immunotoxicity may be required regardless of the Tier of DC.

③ Endocrine activity

No tests specialized to endocrine activity of the subject substance shall be required regardless of Tier of DC of the substance. However, if adverse effects due to the endocrine activity are suspected from available information, test results[10] that provide information on such adverse effects may be required regardless of the Tier of DC.

④ Toxic effects attributed to bioaccumulation

a. Dietary Concentration "Tier I" or "Tier II"

It is not mandatory for the subject substance of this tier to conduct tests that provide information on bioaccumulation. However, such test results may be required for substances considered to be highly bioaccumulative (such as polyhalogenateddibenzo-p-dioxins, polyhalogenated dibenzofuran, polyhalogenated biphenyls, etc.), or for

[9] For example, information related to inhibition of cholinesterase activity, like organophosphate and carbamate compounds.

[10] Appropriate measures shall be considered according to the OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters, taking Tier of DC and suspected adverse effects of the subject substance into consideration.

substances for which it is deemed necessary in view of log Pow value and special consideration (chemical structure, etc.) that raise concerns about bioaccumulation.

b. Dietary Concentration "Tier III"

(a) If log Pow value is less than 3

If there are any special considerations (chemical structures, etc.) that create concerns about bioaccumulation, test results (except subchronic toxicity test) that provide information on bioaccumulation may be required.

(b) If log Pow value is 3 or more

Test results (except subchronic toxicity test) that provide information on bioaccumulation shall be required.

c. Dietary Concentration "Tier IV"

Since results of ADME study are required for "Tier IV", study results shall be used as information on bioaccumulation.

(2) Substances that require special attention (metals, inorganic compounds, mixture of chemical substances)

① For metals, inorganic substances and proteins falling under Dietary Concentration "Tier I", "Tier II" or "Tier III", test results required for "Tier III" shall be required in principle (results of genotoxicity and subchronic toxicity tests). If necessary, results of other toxicity tests and related studies or other relevant information may also be required. For those falling under "Tier IV", test results corresponding to this Tier shall be required in principle (results of genotoxicity, subchronic toxicity, reproductive toxicity, developmental toxicity and carcinogenicity tests, and ADME study).

② For mixtures of chemical substances, the same requirements as ① shall be applied in principle. If there are sufficient information or analytical results that prove the mixture poses no toxic effects that require special attention and contains no substances that require special attention, it shall be possible to conduct an assessment based on results of toxicity tests and related studies or other relevant information required for each Tier of DC.

③ For substances manufactured based on new technologies such as nanomaterials, characteristics of toxicity may be different from those of substances not manufactured based on new technologies. Therefore, an assessment shall be conducted appropriately as necessary.

4. Other

For non-intentionally contained substances in materials of ACP (such as impurities, by-products and decomposition products) that are estimated or identified according to "Article 2. 1. Migration testing", an assessment shall be conducted based on results of toxicity tests and related studies or other relevant information required for each Tier of DC in principle. If it is technically difficult to perform toxicity tests and related studies with a single substance, assessment shall be conducted based on results of toxicity tests and related studies with mixture[11] or in other appropriate manner.

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[11] For example, a mixture extracted from materials of ACP with food simulant or a mixture prepared appropriately in view of feasibility of toxicity tests and related studies (such as that extracted from materials of ACP using a solvent with high extractability).

Article 4: Methods of assessment for Polymeric Additives

If the Assessment-Requested Substance is a polymeric additive, assessment shall be done basically according to the following items 1 or 2, distinguishing the subject substance by whether or not the average molecular weight (weight (Mw)) is 1,000 or less in principle[12]. Concerning matters not described here, descriptions in other items shall be referred.

Methods for assessment in this item are designated as the basic methods for assessment of polymeric additives. In the case of assessment in which particular consideration is explained and such consideration is judged to be reasonable, the assessment shall be possibly done by a method other than that described in this item.

1. If the average molecular weight is 1,000 or less

(1) Findings on migration into foods.

A polymeric additive and its constituent monomers are regarded as subject substances. For these substances, the results of migration testing designated by the Appendix 2 are requested to be provided.

Tier of DC for these substances shall be decided by Dietary Concentrations of migrated fraction of the polymeric additive with molecular weight 1,000 or less and its constituent monomers respectively. If quantity of migration on migrated fraction with molecular weight 1,000 or less cannot be identified, assessment shall be done on the assumption that all migrated polymers are of molecular weight 1,000 or less.

(2) Findings on safety.

Basically, results of various toxicity tests and related studies or other relevant information designated by Article 3, item1, depending on the Tier of DC are requested to be provided for migrated fraction of the polymeric additive with molecular weight 1,000 and less and its constituent monomers respectively. In the case that the subject polymeric additive is composed of fraction of polymers with molecular weight 1,000 or less, the assessment may be done based on results of various toxicity tests and related studies or other relevant information on the polymeric additive itself (unfractionated) in spite of fractionated polymers with molecular weight 1,000 or less.

If the results of the genotoxicity test on constituent monomers of subject polymeric additive are already available, genotoxicity of the polymeric additive may be assessed based on said findings or considering additional findings on its structure-activity relationship.

2. If the average molecular weight is higher than 1,000

(1) In cases where a polymeric additive is not composed of fraction of polymers with 1,000 or less or the composition rate of that fraction is considered sufficiently low.

① Findings on migration into foods. It is not mandatory to provide the results of migration testing designated by Appendix 2.

Nonetheless, results of migration testing designated by Appendix 2 may be requested

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[12] Depending on the characteristics of a polymeric additive, the appropriate average molecular weight used for distinguishing may differ from default of 1,000. In such a case, the substance shall be distinguished based on appropriate molecular weight replaced from default of it considering its polymerization degree and so on, then assessed in accordance with this item. For example, the average molecular weight higher than 1,000 may be appropriate for poly- and per-fluoro compounds. If an assessment is conducted based on the replaced molecular weight, scientific evidences shall be requested judgement on the validity of its replacement.

regarding to a polymeric additive (including its decomposed polymers) and its constituent monomers, in the case where special consideration is considered necessary based on the chemistry information of the polymeric additive (e.g.e.g., in the case where said polymeric additive is hydrolyzed, or its residual monomers are of concern). In this case, assessment shall be done according to the designation in the above mentioned 1. (1).

② Findings on safety.
Regarding constituent monomers of a polymeric additive, it is mandatory to provide results of genotoxicity tests (As for details of the study, refer to Article 3, item 2. (1). ①).
If a migration testing designated by Appendix 2 is conducted, assessment shall done according to the designation in the above mentioned 1. (2).

(2) In cases where above mentioned (1) is not applicable
Both findings on migration of a polymeric additive into foods and findings on safety shall be required according to the designation in above mentioned 1.

(Appendix 1)

Summary of documents necessary for assessment of ACP

The documents listed in the table below shall be necessary for assessment. See Chapter 2: Detailed Exposition, for details on each document.

<table>
<tr><th></th><th colspan="4">Initial assessment[*1]</th><th>Partial revision[*2]</th></tr>
<tr><td>Chemical information for the Assessment-Requested Substance</td><td colspan="4"></td><td></td></tr>
<tr><td>1 Identity</td><td colspan="4"></td><td></td></tr>
<tr><td>(1) Name, structure, etc.</td><td colspan="4">○</td><td>○</td></tr>
<tr><td>(2) Physical and chemical properties</td><td colspan="4">○</td><td>△</td></tr>
<tr><td>(3) Manufacturing method, etc.</td><td colspan="4">○</td><td>△</td></tr>
<tr><td>(4) Others</td><td colspan="4">△</td><td>△</td></tr>
<tr><td>2 Purpose of use and conditions of use</td><td colspan="4"></td><td></td></tr>
<tr><td>(1) Purpose of use</td><td colspan="4">○</td><td>○</td></tr>
<tr><td>(2) Conditions of use</td><td colspan="4">○</td><td>○</td></tr>
<tr><td>3 Draft standards and criteria</td><td colspan="4">○</td><td>○</td></tr>
<tr><td>4 Status of use in Japan and overseas</td><td colspan="4"></td><td></td></tr>
<tr><td>(1) Japan</td><td colspan="4">○</td><td>○</td></tr>
<tr><td>(2) EU</td><td colspan="4">○</td><td>○</td></tr>
<tr><td>(3) United States</td><td colspan="4">○</td><td>○</td></tr>
<tr><td>(4) Other countries</td><td colspan="4">△</td><td>△</td></tr>
<tr><td>5 Assessment in overseas</td><td colspan="4">○</td><td>○</td></tr>
<tr><td>6 Others</td><td colspan="4">△</td><td>△</td></tr>
<tr><td>Findings on migration into foods</td><td colspan="4"></td><td></td></tr>
<tr><td>1 Migration testing</td><td colspan="4">○</td><td>○</td></tr>
<tr><td>2 Dietary Concentration</td><td colspan="4">○</td><td>○</td></tr>
<tr><td rowspan="2">Findings on safety</td><td colspan="4">Tier of DC</td><td rowspan="2"></td></tr>
<tr><td>Tier I</td><td>Tier II</td><td>Tier III</td><td>Tier IV</td></tr>
<tr><td>1 Genotoxicity</td><td>○</td><td>○</td><td>○</td><td>○</td><td rowspan="5">- If Tier of DC of the substance is changed, follow the specification for the initial assessment[*1].
- Toxicity tests may be omitted if there</td></tr>
<tr><td>2 Subchronic toxicity</td><td>△</td><td>△</td><td>○</td><td>○</td></tr>
<tr><td>3 Reproductive toxicity</td><td>△</td><td>△</td><td>△</td><td>○</td></tr>
<tr><td>4 Developmental toxicity</td><td>△</td><td>△</td><td>△</td><td>○</td></tr>
<tr><td>5 Chronic toxicity</td><td>△</td><td>△</td><td>△</td><td>○</td></tr>
</table>

6 Carcinogenicity	△	△	△	○	are no changes of Tier of DC. If new findings are obtained, attach relevant documents.
7 ADME	△	△	△	○	
8 Others					
(1) Neurotoxicity	△	△	△	△	
(2) Immunotoxicity	△	△	△	△	
(3) Endocrine activity	△	△	△	△	
(4) Bioaccumulation	△	△	△	-*3	

○: Documents to be attached

△: Documents to be attached if there is available information or any information is required

*1: Assessment for newly establishing standards and criteria for substances never been assessed on the food safety.

*2: Assessment for revising the previously established standards and criteria.

*3: Use documents on “7 ADME”

(Appendix 2)

Method of Migration testing and calculation method of Dietary Concentration

1. Migration testing

Migration testing shall be done according to the following (1) and (2) for calculation of Dietary Concentration of the subject substance: substances that migrate into foods, due to contact of the foods with ACP, either from the layer that directly contacts to the foods (direct-food-contact layer) or from the layer that not directly contacts to the foods (indirect-food-contact layer). These substances include intentionally used substances as raw materials for materials of ACP, and non-intentionally contained substances in materials of ACP (such as impurities, by-products and decomposition products). Migration testing may be omitted in some cases, as described below. When migration testing is omitted, the reason to omit it and its scientific validity shall be provided.

(Example cases.)

- ○ When the concentration of the subject substance in the food simulant is calculated on the assumption that maximum level of standards (draft) for the amount migrated into the food simulant, migration testing may be omitted[13].
- ○ When existing test results or any other information are available, on the concentration of the subject substance in the food simulant obtained from migration testing conducted under a condition that is equal to or more severe than those provided in these Guidelines, migration testing may be omitted[14].
- ○ If the Assessment-Requested Substance is an additive and is applied to several types of base polymers (e.g. every base polymers in the synthetic resin group (refer to reference in 4 (1) for details)), migration testing on each type of base polymer may be omitted by conducting migration testing on a representative base polymer which has major contribution to exposure to additives through migration (e.g. the base polymer that physical properties facilitate migration of additives, or that Consumption Factor is high). For the case where an additive is applied to every base polymers in a synthetic resin group (except cases where the main usage is application to coating and adhesives), representative polymer of each synthetic resin group and fundamental principle of its selection follow Appendix Table 1.

Appendix Table 1. Representative polymer of each synthetic resin group and fundamental principle of its selection

Synthetic Resin Group (Type of synthetic resin[*1])	Representative Polymer	Fundamental Principle
Group 1	–[*2]	
Group 2 (PS, and other resins of this type)	PS	Consumption Factor in the group is high.
Group 3 (PA, and other resins of this type)	PA	Consumption Factor in the group is high.

[13] In this case, the Dietary Concentration shall be calculated using the calculated concentration in food simulant.

[14] In this case, the Dietary Concentration shall be calculated based on existing test results or available information on the concentration in food simulant.

Group 4 (PVC, PVDC)	Soft PVC	Consumption Factor in the group is high. Physical property of the resin facilitate migration of additives.
Group 5 (PE)	Low density PE	Physical property of the resin facilitate migration of additives.
Group 6 (PP)	Random PP	Physical property of the resin facilitate migration of additives.
Group 7 (PET)	Non-crystallized PET	Physical property of the resin facilitate migration of additives.

*1: PS (polystyrene), PA (polyamide), PVC (polyvinyl chloride), PVDC (polyvinylidene chloride), PE (polyethylene), PP (polypropylene), PET (polyethylene terephthalate)
*2: Polymers in Group 1 will be concerned individually.

○ If the Assessment-Requested Substance is a base polymer and its physical and chemical properties can be judged to have high similarity to those of other base polymers in the same synthetic resin group to which it belongs, migration testing of approved additives for said synthetic resin group may be omitted, when these additives are applied to the base polymer of Assessment-Requested Substance. Moreover, for the case where high similarity of the physical and chemical properties cannot be judged, migration testing of approved additives may be omitted, when these additives are comprehensively judged[15] not to have a large effect on exposure.

(1) Test method and sample

① Test method

Migration testing shall be done by immersion method in principle. If other methods are considered to be appropriate, however, the one-side elution method or filling method shall be used as described below.

(Example of cases in which a method other than immersion method is deemed appropriate)

- When the Assessment-Requested Substance is used for indirect-food-contact layers of multi-layer materials of ACP.
- When the Assessment-Requested Substance is used in ACP with restricted thickness or shape.

For details of manipulations for one-sided elution method and filling method, refer to "Standard Methods of Analysis for Hygienic Chemists with Commentary (The Pharmaceutical Society of Japan)" and "Standard Methods of Analysis in Food Safety Regulation (Japan Food Hygiene Association)". When PPO (poly (2,6-diphenyl-p-phenylene oxide))[16] is used, an Annex of this Appendix shall be referred for details of manipulations.

[15] Judgement shall be based on consideration of Consumption Factor, physical and chemical properties of the base polymer of the Assessment-Requested Substance, and results of migration testing conducted using several representative additives. When Consumption Factor is focused on, spreading potential of the ACP produced with the said base polymers shall be also considered depending on the purpose of use.
[16] A white particulate matter used as food simulant.

② Test Sample

a. If the Assessment-Requested Substance is a base polymer, test samples of a synthetic resin made with that base polymer shall be prepared. If the Assessment-Requested Substance is an additive, test samples of synthetic resin intended for use shall be prepared by adding the maximum amount of usage of the additive (the maximum amount if the amount in material is limited, or the maximum amount under general condition of use if the amount in material is unlimited). Test samples of synthetic resin containing not only the Assessment-Requested Substance but also others (such as other additives) may be prepared as necessary.
b. A test sample for migration testing shall be one of synthetic resin with physical property due to which additives etc. shall migrate easily from it under the condition of use for the Assessment-Requested Substance. If shape of ACP is limited, a test sample with a shape where additives etc. migrate easily shall be used, among shapes within the limit, for migration testing.
c. Test samples for migration testing, shall be a thin layer of approximately 1 mm thick in principle. If migration testing is conducted using one-sided elution method or filling method, test samples may be a thin layer of approximately 0.5 mm thick in principle. If it is technically difficult to prepare a test sample of above-mentioned thickness due to the processing characteristics of the synthetic resin, a test sample may be prepared with a technically feasible thickness. In addition, if the thickness of ACP shall be restricted despite that the above-mentioned thickness is technically feasible, a test sample with thickness of maximum within relevant restriction may be used.

(2) Test conditions

① Food category and food simulant

a. Migration testing shall be conducted using food simulant designated for each food category for which ACP manufactured with the Assessment-Requested Substance are used. Definitions of each food category and food simulant to be used for each category are summarized in Appendix Table 2. When using a food simulant, the following notes should be considered.
   (a) When foods for which ACP are used fall under the definitions of multiple food categories, food simulants that are fit for all relevant categories shall be used.
   (b) If ACP are used only with dried foods (D_{1sub}) among ordinary foods (D_1), PPO shall be used as food simulants.
   (c) For oils, fats, and fatty foods, 95% ethanol (volume%), isooctane or heptane may be used in place of vegetable oil[17].
b. For food categories for which ACP are not used, if any, migration testing using food simulant corresponding to the categories may be omitted.

Appendix Table 2. Food Categories and Food Simulants

Symbol	Food category		Food simulant
D_1	Ordinary foods	Foods not falling under D_2, D_3, D_4 and D_5	Distilled water
D_{1sub}	Dried foods	Foods of $D_1$with water content of	PPO[*1]

[17] When using vegetable oil, performance of analysis may be insufficient because of interference by ingredients and impurities in vegetable oil or increasing uncertainty by pretreatment for analysis.

		20% or less (weight%) within it or on the surface of it	
D_2	Acidic foods	Foods having a pH 4.6 or less within it or on the surface of it	4% acetic acid (volume%)
D_3	Alcoholic foods	Beverages with an alcohol content of 1% or more (volume%) within it or on the surface of it	20% ethanol (volume%)
D_4	Milk and dairy products	Foods with fat content of less than 20% (weight%) within it or on the surface of it, among foods subject to Article 2 of Ordinance on Milk and Milk products Concerning Compositional Standards, Etc. (Ordinance of the Ministry of Welfare, No.52, 1951; hereinafter refer to as Ordinance on Milks).	50% ethanol (volume%)
D_5	Oils, fats, and fatty foods	Foods with fat content of 20% or more (weight%) within it or on the surface of it (including those subject to Article 2 of Ordinance on Milks and not falling under D_4)	Vegetable oil*2

*1: Applicable when ACP are used only for dried foods (D_{1sub}) among ordinary foods (D_1)
*2: 95% ethanol (volume%), isooctane or heptane may be used in place of vegetable oil.

② Preparation method of food simulant

Preparation method of food simulant shall be pursuant to the provisions concerning reagents and test solutions in “3. Apparatus, Containers and Packaging” of the "“Standards and Criteria for Food and Food Additives, Etc.” of the Food Sanitation Act (Public Notice of Ministry of Health and Welfare No. 370, 1959; hereinafter refer to as Public Notice on Standards and Criteria.). For PPO, the substance with particle size of 60 mesh to 80 mesh, average pore size of 200 nm shall be used. For vegetable oils such as olive oil and rapeseed oil, appropriate one shall be used in consideration of the influence of its ingredients and impurities on analysis.

③ Usage volume of food simulant

In principle, 1.5 mL to 2.0 mL of food simulant shall be used per unit surface area (1 cm^2)[18] where a test sample contacts directly with food simulant for migration testing. However, this does not apply to migration testing where the filling method is used. When PPO is used as a food simulant, the usage volume shall follow the provisions for the testing

[18] Unit surface area is calculated by dimension surface of the test sample. When using the immersion method, sample surface area is a total surface area of both sides of the test sample.