Provisional translation

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Expert Committee on Pesticides
The Food Safety Commission

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Guideline for the assessment of the effect of pesticide residue in food on health

Article 1. General Provisions

Pesticides are used to protect crops against insects, weeds, fungi and other pests in accordance with the Agricultural Chemicals Regulation Law (Law No. 82 of 1948). Trace amount of pesticides may remain in food commodities from plants, livestock and fish, leaving in a potential risk for consumers via intake of residue levels of pesticides through foods. Food Safety Commission of Japan (FSCJ) has conducted the assessments of the effect of pesticide residues contained in food on health (hereinafter referred to as “risk assessment”).

This guideline was compiled based on the FSCJ’s assessment results obtained after the establishment and the principles of the risk assessment on pesticide residue in Japan and international/national organizations. In principle, the FSCJ will conduct the risk assessment on pesticide residue based on this guideline.

Article 2. Objective

This guideline aims at clarifying data needed for the risk assessment and at ensuring consistency of the assessment methodologies among policies/categories for risk assessment. It also aims at ensuring as much international alignment as possible among risk assessment methodologies to secure transparency and smooth facilitation.

Article 3. Definition

3.1. Pesticide (agricultural chemicals as a synonym)

Chemical agents[*1] (agricultural chemicals) that are designated by Article 2, paragraph 1 of the Agricultural Chemicals Law.

3.2. Active Substance

The substance[*2], about which the Ministry of Health, Labour, and Welfare (MHLW) may request a risk assessment and opinion in accordance with the Food Safety Basic Act (Act No.48, 2013). Such assessments are to be used for establishing standards such as the maximum residue limits (MRLs) for agricultural chemicals based on the Food Safety Basic Act (Act No.48, 2013).

3.3. Provisional Standards

Provisional residue standards has been established since the introduction of the positive list system. The pesticides under the provisional standards are those that have not been assessed by the FSCJ yet, but provisional standards were available by referring to the international/national standards, in accordance with the partial revision of the Specification and Standards for Food, Food Additives, etc. (MHLW Notification No.499, 2005).

3.4. Re-evaluation

Re-evaluation is the periodical evaluation of pesticides that are registered in Japan, in accordance with Article 8, paragraph 1 of the Agricultural Chemicals Regulation Law.

[*1] Chemical agents (agricultural chemicals) are defined as follows.

・Fungicides, insecticides, herbicides, and other agricultural chemicals (i.e. Those produced by using the registered agricultural chemicals as materials or ingredients. Agents to control pests stipulated by the cabinet ordinance) that are used to control bacteria, nematodes, mites, insects, rodents, weeds, and other animal, plants, or viruses (hereinafter referred to as pests) with potential to damage agricultural products including trees and agricultural/forestry products (hereinafter referred to as agricultural products and others).

・Plant growth promoters and regulators that are utilized to increase or control the physiological functions, germination inhibitors, and other chemicals, but excluding the fertilizers stipulated in Article 2, paragraph 1 of the Fertilizer Regulation Law.

[*2] Ingredients in agricultural chemical products include active ingredients and impurities (contaminants).

Article 4. Basic approach to risk assessment on pesticide residues

4.1. Codex Alimentarius Commission has defined in its “Working Principles for Risk Analysis for Food Safety for Application by Governments” (CAC/GL 62-2007) that the risk assessment should be

conducted by the following four steps: hazard identification, hazard characterization, exposure assessment, and risk characterization (Ref. 1).

FSCJ will conduct risk assessment focusing on hazard identification and characterization, because risk managing styles are widely diverse among a pesticides.

4.2. The assessment is basically conducted in accordance with “Principle and Methods for the Risk Assessment of Chemicals in Food” (Environmental Health Criteria 240) (Ref. 2). When it is difficult to make a judgement based on these criteria, expert judgement will be requested.

4.3. In principle, the following studies and/or data are required for the risk assessment.

1) For pesticides that are applied for new registration in accordance with the Agricultural Chemicals Regulation Law, the assessments are conducted by using the data on toxicity studies submitted by the applicant upon registration request.
2) For pesticides that are currently managed under the provisional standards (MRLs), the assessments are conducted by using the summary reports or summary dossier submitted by the applicants, or by using reports of risk assessments conducted by international/domestic organizations (Ref. 3 and Ref. 4).
3) For pesticides applied in line with the guideline requirements for an import tolerance to obtain (setting of) MRLs, the assessment is conducted using data on toxicity studies submitted by the applicants.
4) For specified pesticides as stipulated in Article 3, paragraph 1 of the Agricultural Chemicals Regulation Law, and for the chemicals exempted from setting the MRLs (so-called exempt substances) as stipulated in Article 11, item 3 of the Food Hygiene Law, The assessment is conducted to determine whether the pesticide has a potential of adverse effect on health for human exposed to it at residue levels in foods or not, when used properly (Ref. 5 and Ref. 6).
5) When the FSCJ judges that additional studies, data and/or comments are needed from the applicants for the assessment, the FSCJ requests their submission to risk managers.

4.4. Currently, international consensus of consideration on genotoxic carcinogens[*3] is still not formed. In the meantime, until such a consensus is made, the FSCJ will proceed with condition that there is no thresholds in such agents.

To identify whether or not a substance is likely to be a genotoxic carcinogen, careful consideration is essential over the mechanism (mode) of action and others.

4.5. Pesticides contain active ingredients and impurities. They are metabolized and degraded after its application in plants, then possibly consumed through food intake. Therefore, the assessment needs consideration of metabolites /degradants or impurities.

4.6. Human data (study and/or information) are considered valuable, however their reliability should be verified comprehensively before using in the assessment.

[*3] In this guideline, a genotoxic carcinogen is defined as a chemical or its metabolite that reacts directly with DNA, resulting in becoming a part of the carcinogenicity mechanism. The reaction results include DNA damages, chromosomal aberration, and gene mutation. To confirm genotoxicity, *in vivo* studies are recommended (at the target organ of carcinogenicity if possible).

Article 5. Evaluation on safety data (i.e. studies and/or information) of agricultural chemicals

5.1. In principle, studies and consideration points needed for evaluations are described in the Appendix Table 1 in compliance with the MAFF guideline. In general, testing methods for these studies should be in accordance with the MAFF test guidelines or the internationally recognized test guidelines such as that of OECD.
Certain pieces of studies would not be necessary in the following cases:

1) When there is adequate scientific evidence to show that the substance of a pesticide is broken down in the food or in the gastrointestinal tract and become common food constituents.
2) A case where the FSCJ has reasonable evidence over the newly applied pesticide, such as that the chemical structure is similar to a previously assessed pesticide except the base.

When several data sets of studies for evaluation of single pesticide are submitted by several applicants due to independent registrations, and their specifications of pesticide technical are judged to be qualitatively equivalent, then the pesticide can be assessed using all data compiled.

5.2. Submission and quality assurance of data for the assessment is responsibility of applicants of the pesticides.

In principle, the submitted data need to meet the following quality: the studies that are conducted in compliance with GLP, the studies that are conducted in accordance with the OECD test guidelines, or that are in line with the other test guidelines. Submitted data also include scientifically reliable information such as risk assessment reports by the international organizations.

In addition, the FSCJ requests submission of all available information on toxicology or kinetics if they are not listed in the Appendix Table 1.

5.3. The Expert Committee on Pesticides uses published literatures submitted by risk managers for the assessment after the Committee judges them to be suitability for use (Ref. 8).

Article 6. Assessment

6.1. Interpretation of metabolism studies in plants and animals

Information on metabolism and residues in plants and animals is important because the FSCJ conducts a risk assessment of pesticide residues in foods. Metabolism data in experimental animals are useful for understanding the mechanism of toxicity. Consumers potentially ingest a metabolite/degradate of a pesticide produced in plants/animals via their absorption, distribution, metabolism and elimination. Not only the parent pesticides but also their metabolites/degradates are evaluated if necessary.

6.2. Specifying no-observed-adverse-effect level (NOAEL) and interpretation of toxicity data

1) Comprehensive consideration is necessary for interpretation of data.

The no-observed-adverse-effect level (NOAEL) is specified by using endpoints such as of general observations of animals, body weights, feed consumptions, hematology, blood biochemistry, urinalysis, and histopathology. Statistical and dose-related significances are logically and scientifically taken into account to set NOAEL. At the specification, kinetics or species used in toxicity studies or dose-spacing of studies should be considered. Mode of action (MoA) of toxicity should be made clear as much as possible, and relevance of the toxicity to humans is valuable.

2) When multiple studies are conducted by using the same species, or when a common MoA toxicity is observed among multiple species, an overall NOAEL can be specified by using the relevant studies after consideration over suitability of their study designs and results.
3) The 1st group of Expert Committee on Pesticide will establish the general perspectives where common interpretation is necessary at assessments (Ref. 9 and Ref. 10).

6.3. Establishment of an ADI

An acceptable daily intake (ADI) is established as a guidance value that is reasonable in terms of long-term dietary intake effect on human health by pesticide residues in foods. Basic principles at ADI establishment are as followings:

1) If multiple NOAELs are identified from toxicity studies, the lowest NOAEL should be chosen for setting an ADI, based on comprehensive assessments on toxicological profiles of the pesticide. The lowest value is the most sensitive POD for the pesticide, so most rational to be the ADI.
2) A safety factor of 100 is generally applied for establishing an ADI based on considering species and individual differences. The value 100 is not necessarily representative, fixed value. Alternative value can be applied as a safety factor depending on the type of toxicity or study as follows.
   ① When data from human studies are used, the species difference does not need to be accounted for. A safety factor of 1 to 10 for individual difference is applied to cover the variability in the study population.

② An additional safety factor of 1 to 10 can be applied depending on the appropriateness of the study design, sufficiency of toxicological information, and severity of toxicological profiles.

③ When an ADI is established based on a LOAEL, an additional safety factor of 1 to 10 should be applied.

3) "ADI not specified" can be applicable to a substance that either has a very low toxicity, or is rapidly metabolized/excreted thus extremely unlikely to be accumulated. This applies to the substance, with which ADI is established. Clear explanation on toxicity and residual information should accompany to this designation.

4) When the risk managers are in charge of several pesticides that have a com MOA and similar toxicity at same doses and when the managers request their risk assessments as group ADI of these pesticides should be prepared. To apply this adequate data set of studies to assess individual pesticides, a group ADI should be set after a comprehensive judgement is done on comparison of various study results among the pesticides.

6.4. Setting of Acute reference dose (ARfD)

An acute reference dose (ARfD) is a health guidance value of pesticide residue for short-term high-amount intake of a food commodity for human (Ref. 11).

6.5. Definitions of residue for dietary risk assessment

Residue for dietary risk assessment is identified based on the studies of metabolism/degradation and residues in animals/plants/the environment, and toxicology. Furthermore, dietary intakes estimation of chemicals set as residue definition should be carried out as much possible for dietary risk assessment (Ref. 12).

Article 7. Revised assessment/evaluation

A revision of assessment/evaluation of pesticide residue should be conducted based on the latest scientific quality when risk managers request revision of assessment or re-evaluation (the latter carried out in compliance with Article 8 of the Agricultural Chemical Regulation Act) of a pesticide residue, or when the FSCJ judged a revision of toxicological evaluation necessary after obtaining new information of studies, or in light of shift in international criteria on risk assessment (Ref. 13).

Article 8. Up-dating of guidance

This guideline should be revised as the FSCJ sees it necessary, based on the latest trend of international criteria on risk assessment and scientific evidence.

Appendix 1. Items to be included in a risk assessment report for evaluation of an active substance

		New*[1]
General information of pesticides		
	・ Usage	○
	・ General name of the active substance	○
	・ Chemical name	○
	・ Molecular form	○
	・ Molecular weight	○
	・ Chemical structure	○
	・ History of development/mechanism as pesticide	○
Studies related to safety		
	・ Animal metabolism	○
	・ Plant metabolism	○
	・ Fate and behavior in the environment	○*[2]
	・ Residues in soil	○*[2]
	・ Residues in crops	○
	・ Livestock metabolism, and residues in livestock	△
	・ Acute toxicity	○
	・ Subacute/subchronic toxicity	○
	・ Chronic toxicity/carcinogenicity	○*[3]
	・ Reproductive developmental toxicity	○
	・ Battery studies on genotoxicity	○
	・ Other studies (general pharmacology, neurotoxicity, immunotoxicity, pesticidal mechanism, irritancy tests to the eye or the skin, and others)	△
	・ Human data	△

○：Documents to be submitted by applicants

△：Documents (i.e. all available studies and data/information on new findings) to be submitted by applicants when requested (i.e. the applicant has new data/information available).

*1：When implementing registration review, excluding re-evaluation, for a pesticide already established the ADI and ARfD, only information necessary for the last registration should be submitted by applicants.

*2：The mark △ is for the import tolerance application.

*3：For a chronic toxicity study using dogs, refer to a guidance for “one-year repeated toxicity study in dogs for the toxicological evaluation of pesticides (Decision of the Expert Committee on Pesticide, FSCJ, 21 December 2017) (Ref. 7).