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Expert Committee on Pesticides
The Food Safety Commission

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Guide for considerations on residue definitions for dietary risk assessments of pesticide residues

Section 1. Introduction

Pesticides, after its application, are metabolized/degradated in plants, animals, and environmental fields such as soil and water. Their remaining concentration declines with time. Though this process, the subsequent chemicals may maintain a similar toxicity or become more toxic compared to the parent pesticide. People might be exposure to such metabolites/degradates via foods from plants, animals or seafood, etc.

For the risk assessment of pesticide residues, it is important to consider toxicology and exposure aspects of parent pesticides as well as their concerned derivatives for human health through foods. If necessary, an acceptable daily intake (ADI) and/or acute reference dose (ARfD) should be set for these chemicals. This document is to give a guidance of how to determine a residue for dietary risk assessments at the Expert Committee on Pesticides, Food Safety Commission of Japan.

The contents of this document are prepared based on the currently available scientific information. When a new methodology of residues or toxicology on its metabolites/degradates established, or scientific evidence is sufficiently accumulated on metabolite/degradate, the corresponding parts of this document will be updated as well. The list of previously set chemicals for dietary risk as the corresponding part of the guide will be accordingly modified.

Section 2. Definition of terms

2-1. Metabolite and degradate

A chemical that is produced from the parent pesticide through metabolism or degradation inside plants and animals, plant surface or soil.

2-2. Residue definition for dietary risk assessments

All substances, among those listed in ‘metabolite and degrade’ above, are to be taken into consideration for the dietary risk assessment of pesticide residue.

Section 3. Approach for consideration on a residue definition for dietary risk assessment

Pesticides are expected to be metabolized/degradated by various reactions in plants, animals and fish. Kinds and quantity of metabolites/degradates presumably vary. Therefore, residue definitions for dietary risk assessment should be individually deliberated for agricultural products, livestock and fish.

Section 4. Studies used for the consideration

For dietary risk assessment, it is preferable to use studies that are equivalently high quality and quantity to the studies used for the parent pesticide. However, often times, only limited number of study results are available for such determination. Therefore, in addition to using tests described below, other available data should be also looked into as much as possible. Toxicology database on chemicals are helpful, thus those can be referred to as well.

4-1. Studies needed for consideration of exposure metabolites/degradates amounts (where a parent pesticide is used for the experiments.)

① Metabolism study in experimental animals (rats, mice)
② Metabolism study in livestock animals (goats, cows, and hens)
③ Metabolism study in plants
④ Study of residues in crops (including rotational crop residue studies)
⑤ Feeding study for residue in livestock animals and milk from daily cows

4-2. Studies needed for toxicity consideration on metabolites/degradates (in either a parent pesticide or its metabolites/degradates are used in the studies)

① Oral acute toxicity study
② Genotoxic study
③ Other toxicity studies (if already available studies exist.)

Section 5. Steps for consideration

Steps for the consideration is shown in Figure 1. Details are explained below.

Section 6. Consideration of exposure amounts (See Step 1 in Figure 1)

Metabolites/degradates, indicated below, are targeted as residues for dietary risk assessment.

6-1. In foods of plant origin

① Metabolites/degradates that shows more than 10% of total residual radioactivity (TRR) in edible

parts from plant metabolism studies, and significant amount residue is detectable in crop residue trials.

② Metabolites that show more than 10% of TRR from plant metabolism study, and significant residues are detectable in parts used for feeds of livestock feed (straws of rice, wheat, and corn) from crop residue trials.

③ If metabolites are found in rodent ADME study, their toxicities might be comprehensively covered by the parent toxicity. In such cases, such metabolites may be excluded from the evaluation, depending on their toxicity.

6-2. In livestock and livestock products

① Metabolites that have more than 10% of TRR in edible parts (milk, egg, muscle) from livestock metabolism studies, and detectable at significant amount from feeding studies.

② If the metabolites are detectable in rodent ADME study, their toxicities might be covered by the parent toxicity. In such a case, evaluation of the metabolites is not needed. However, metabolites that are livestock-specific or are produced at significant amount should be still evaluated

③ For results of studies with feeding regimen of parent product that produces similar level of actual residue should be both considered in the livestock.

④ When both the livestock metabolism studies using 2 species (commonly goats and hens) and the residue studies of livestock using 2 species (commonly goat and hen) are available, residue definitions for dietary risk assessment in animal commodities should be considered. But even when both metabolism and residue studies are available, following 2 conditions allow the consideration on residue definitions for dietary risk assessment in animal commodities.

A. When 2 metabolism studies are conducted in livestock, and the amount of metabolite showing TRR of more than 10% is either non-present or only very low.

B. When a pesticide use is limited to the feeding crops of ruminant or poultry, and its livestock metabolism study has been conducted in using ruminant or poultry, in addition to meeting the following 2 conditions:

   a) A livestock residue study has been conducted.

   b) Although a livestock metabolite study is not conducted, studies have shown that metabolites have no more than 10% of TRR or only low in a livestock metabolism study.

6-3. In fish

At present, the maximum estimated residue levels are calculated based on a predicted environmental concentration (PEC) and bioconcentration factor (BCF), in accordance with definition methods for residue levels in fish (Health and Labor Science Research Grant, 2007 (H14)), which was conducted at the time when positive list system of pesticide was introduced in Japan. Usually enough information is not available for metabolites in fish. Consideration on metabolites is only limited to the occasions when enough information is available.

Step 7. Consideration of toxicology (See Step 2 in Figure 1)

7-1. Toxicity of metabolite/degradate is assessed by its proportional potency to that of the parent pesticide. The toxicity of metabolite/degradate is assessed as strong, similar or weak to the parent pesticide.

7-2. When the lethal dose (LD) 50% of a parent pesticide is higher than 2000 mg/kg bw and its metabolites have the same degree of toxicity, it is not basically necessary to consider toxicological evaluation of metabolites/degrade of the pesticide. A chemical of 2000 mg/kg bw of LD_{50} is recognized as a low toxic substance (judged that human health effect is unlikely). The dose of 2000 mg/kg bw is also accepted as an upper limited dose of oral administration.

7-3. When a toxicity of a metabolite/degradate is weaker than that of its parent pesticide by LD_{50} values, consideration on toxicology is not necessary. However, careful handling is needed when the parent pesticide shows strong toxicity, then its metabolites also have strong toxicity.

Section 8. Consideration of setting ADI/ARfD for metabolites/degradates (See Step 3 in Figure 1)

8-1. When a metabolite/degradate shows a stronger toxicity than its parent pesticide (especially, when its metabolite/degradate is the active substance of the toxicity), or when a metabolite/degradate shows different toxicological characteristics (profiles/endpoints) from its parent, the ADI/ARfD of metabolite/degradate should be set separately from its parent chemical, or the combined ADI/ARfD of parent chemical and its metabolite/degradate should be established. In provision to those cases, adequate data set is necessary to acquire appropriate toxicological evaluation (such as the chronic toxicity study).

8-2. When a metabolite/degradate toxicity is judged to be as similar to its parent pesticide, the ADI/ARfD of the parent pesticide plus metabolite/degradate can be set, based on the no-observed-adverse-effect level (NOAEL) of the parent pesticide.

Section 9. Points to note

9-1. Conjugates that are produced need careful handling in relation to their potential de-conjugation in animal body and production of further metabolites afterward.

9-2. When a residue level is assessed, following points should be comprehensively considered: toxicological severity; detection ratio of the parent pesticide and the metabolite/degradate; difficulty of analysis.

9-3. Handling of metabolites/degradates is decided based on scientific evidence of exposure and

toxicology. Especially careful considerations are required for the following cases:

① When residue is known to concentrate in specific crop species or certain parts of the crop.

② When the parent pesticide and its metabolites/degradates are both known to be low in toxicity, thus toxicological consideration is not needed for metabolite/degradate, but the quantity of metabolites/degradates exceeds that of parent pesticide. This includes a unique metabolite/degradate found in genetically modified (GM) crops.

③ When human health effect is predicted by a metabolite/degradate. The foreseen cases include metabolite/degradate of less than 10% TRR in any metabolism studies, but the metabolite/degradate has a higher toxicity or more accumulative property than its parent pesticide, based on the chemical structures, and the metabolite/degradate that are produced from a parent pesticide of particularly high toxicity.

9-4. Where a metabolite/degradate is further predicted to exert a new toxicity, the additional data may be requested depending on the situation.

9-5. 'Information of residue definition for dietary risk assessment' by the foreign risk assessment organizations (JMPR, USEPA, EFSA, etc.) should be referred to, when these evaluation matters are considered.

Section 10. Documentation of the risk assessment report

Clearly documentation of the following pieces of information should be ensured: a chemical defined as a residue definition for dietary risk assessment as it remains in commodities from plants; livestock or fish, thus raise some concern of adverse effects on human health; the reasons of such choice; the reasons of its choice to set the ADI/ARfD. The summary should also contain residue defined for dietary risk assessment.

In order to make clear of the information necessary for the consideration above, the information stated below should be included in the section of the food effect assessment on health.

10-1. Metabolism study in experimental animals

Summary of metabolite/degradate found in metabolism studies in rats and mice, which are found more than 10% TRR in the metabolism studies in livestock and/or plants.

10-2. Metabolism study results in livestock

① Main chemicals

② Metabolites found to have more than 10% TRR, including residues.

10-3. Metabolism study results of plats

① Main chemicals

② Metabolites with more than 10% TRR in edible parts.

③ Metabolites that are found to have more than 10% TRR in parts of plants that are used for feed (straws of rice, wheat and corn), including their residue amounts.

10-4. Residues in crop

Maximum residual levels from studies to analyze a metabolite/degradate.

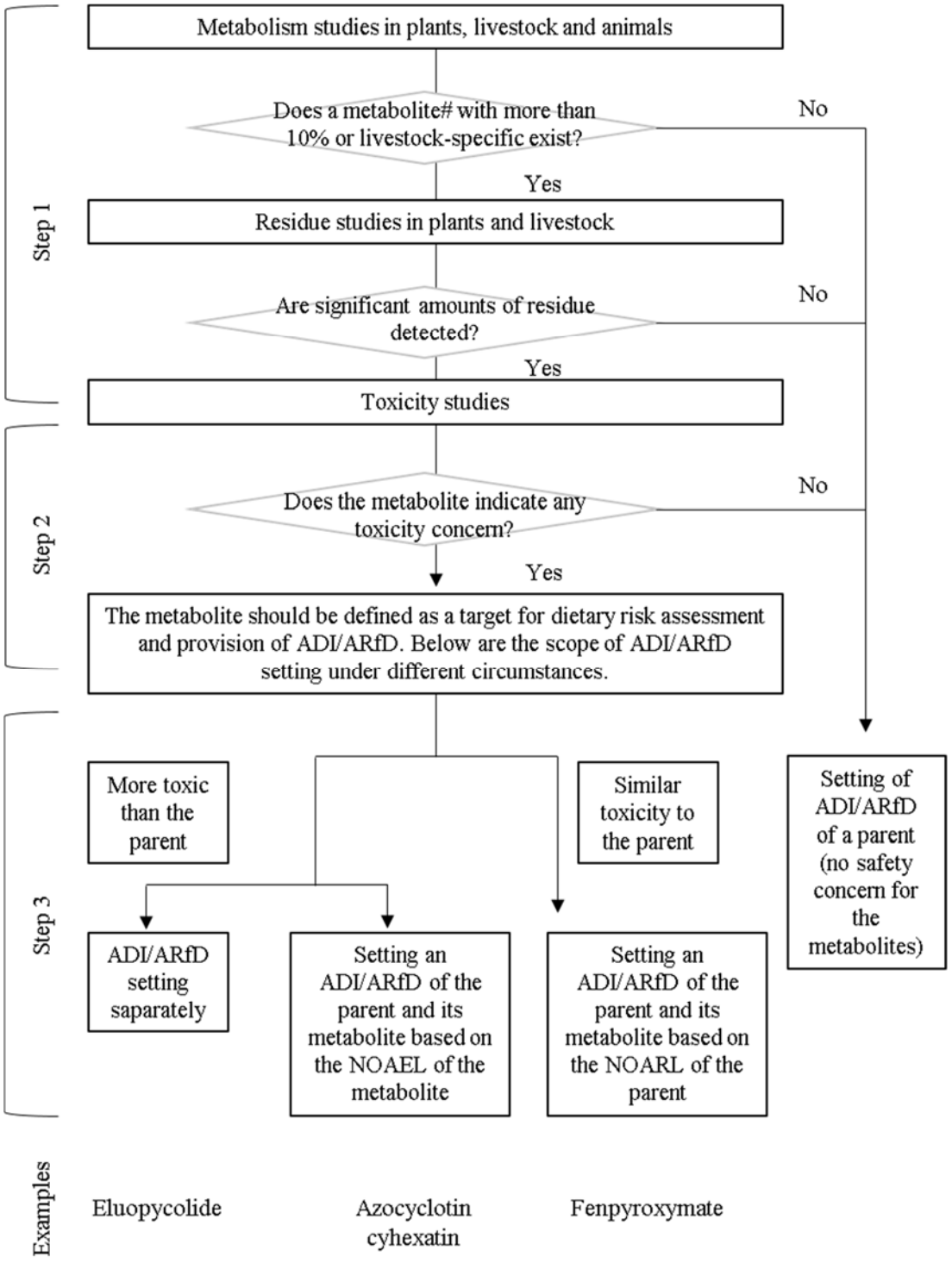
10-5. Study results in livestock

Maximum residual levels from studies to analyze a metabolite/degradate.

10-6. Study results in fish

Maximum residual level from a metabolite/degradate analyzed.

Figure 1. Consideration on residue definitions for dietary risk assessment



#Metabolite/degradate expressiong as metabolite in this figure