

Regarding Establishment of the “substances to be determined by the Minister of Health, Labour and Welfare as those that apparently have no potential to cause damage to human health” as Specified in Article 11, Paragraph 3 of the Food Sanitation Law (Draft)

The execution of Article 11, Paragraph 3 of the Food Sanitation Law requires the establishment of the “level to be determined by the Minister of Health, Labour and Welfare, at the Pharmaceutical Affairs and Food Sanitation Council’s advice, as that having no potential to cause damage to human health” and the “substances to be determined by the Minister of Health, Labour and Welfare as those that apparently have no potential to cause damage to human health” as specified in the same paragraph, in accordance with the preparation of the standards (including provisional standards) pursuant to Article 11, Paragraph 1 of the same law.

Regarding, among these, the “substances to be determined by the Minister of Health, Labour and Welfare as those that apparently have no potential to cause damage to human health”, this paper summarizes possible ideas for establishing such substances.

I. Legislative background

Article 11, Paragraph 3 of the revised Food Sanitation Law

Food⁶ in which residues of any agricultural chemicals¹ (meaning agricultural chemicals stipulated in Article 1-2, Paragraph 1 of the Agricultural Chemicals Regulation Law (Law No.82 of 1948); hereinafter the same applies in the following article), materials added to, mixed in, soaked into or otherwise used in feed (meaning feed specified in Article 2, Paragraph 2 of the Law for Safety Assurance and Quality Improvement of Animal Feed (Law No.35 of 1953))² for any of the purposes specified in the Ministry of Agriculture, Forestry and Fisheries Ordinance issued pursuant to Article 2, Paragraph 3 of the same law, or substances that are ingredients of medical drugs for use in animals³ specified in Article 2, Paragraph 1 of the Pharmaceutical Affairs Law (including substances formed by chemical changes of such substances, and excluding substances to be determined by the Minister of Health, Labour and Welfare as those that apparently have no potential to cause damage to human health⁴) are found at levels above the level to be determined by the Minister of Health, Labour and Welfare, at the Pharmaceutical Affairs and Food Sanitation Council’s advice, as that having no potential to cause damage to human health⁵ shall not be produced, imported, processed, used, cooked or stored for sale, or sold; provided, however, that the foregoing shall not apply in cases where the specifications for food ingredients as stipulated in Paragraph 1 have been established with regard to the limits of residual levels of such substances in food of interest⁷.

1-3, substances subject to a positive list system (agricultural chemicals, feed additives, and animal drugs); 4, substances not subject to a positive list system; 5, the uniform limit; 6, the extent of application (treatment of processed food); 7, residue standards (including provisional standards)

The “substances to be determined by the Minister of Health, Labour and Welfare as those that apparently have no potential to cause damage to human health” (hereinafter referred to as the “exempted substances”) are, of agricultural chemicals, feed additives and animal drugs (hereinafter referred to as “agricultural chemicals, etc.”) that may remain in food, those that are not subject to the provisions that prohibit the sale, etc. of food containing residual agricultural chemicals, etc. at levels above the “level to be determined by the Minister of Health, Labour and Welfare, at the Pharmaceutical Affairs and Food Sanitation Council’s advice, as that having no potential to cause damage to human health” (hereinafter referred to as the “uniform limit”).

Exempted substances are exempt from regulation because their use as agricultural chemicals, etc. during the production, etc. of agricultural, livestock or aquatic products results in residues in food that apparently have no potential to cause damage to human health, considering the condition and extent of such residues.

II. Treatment under the Agricultural Chemicals Regulation Law and related matters

(1) Provisions in the Agricultural Chemicals Regulation Law

(i) Treatment of the specified agricultural chemicals

Article 2, Paragraph 1 of the Agricultural Chemicals Regulation Law stipulates that no registration by the Minister of Agriculture, Forestry and Fisheries shall be required in “cases of the production or processing, or the importation, of agricultural chemicals to be designated by the Minister of Agriculture, Forestry and Fisheries and the Minister of Environment as those that apparently have no potential to cause damage to crops, etc., humans, livestock or aquatic organisms considering their ingredients (hereinafter referred to as ‘specified agricultural chemicals’).” Vinegar, baking soda, and natural enemies collected around the site of application have already been designated as specified agricultural chemicals. The Ministry of Agriculture, Forestry and Fisheries and the Ministry of Environment determined the “Guidelines on Assessment for the Designation of Specified Control Materials (Specified Agricultural Chemicals)” in March 2004 (hereinafter referred to as the “Guidelines on Specified Agricultural Chemical Assessment”).

The “Guidelines on Specified Agricultural Chemical Assessment” require that safety to humans and livestock be assured by data from: (a) acute oral toxicity studies; (b) mutagenicity studies; (c) 90-day repeated dose oral toxicity studies; and (d) in cases of substances for which adverse effects have been reported, exposure assessment studies.

(Reference) The Agricultural Chemicals Regulation Law (Law No.82 of 1948)

Article 2 A producer or an importer shall not produce or process, or import, any agricultural chemical without registration of such agricultural chemical at the Minister of Agriculture, Forestry and Fisheries; provided, however, that this shall not apply to cases of the production or processing, or the importation, of agricultural chemicals to be designated by the Minister of Agriculture, Forestry and Fisheries and the Minister of Environment as those that apparently have no

potential to cause damage to crops, etc., humans, livestock or aquatic organisms considering their ingredients (hereinafter referred to as “specified agricultural chemicals”), cases of the importation of an agricultural chemical that is involved in the registration mentioned in Article 15-2, Paragraph 1 and that has a notice as stipulated in the provisions of Article 7 applied mutatis mutandis under Article 15-2, Paragraph 6, and other cases to be designated by the Ministry of Agriculture, Forestry and Fisheries Ordinance and the Ministry of Environment Ordinance.

- (ii) Currently, agricultural chemicals which have been registered under the Agricultural Chemicals Regulation Law and for which no standard for withholding of registration is established include the following:
 - (a) Those falling under foods or food additives
E.g. Rapeseed oil, starch, sodium oleate, metal silver
 - (b) Those falling under microbial pest control products
E.g. BT
 - (c) Those falling under natural enemies
E.g. *Franklinothrips vespiformis*, *Diglyphus isaea*
 - (d) Those that have no potential to remain in food due to their uses, such as seed disinfection
E.g. Ipconazol

(2) Treatment under the Food Safety Basic Law

Examples of substances on which a health impact assessment of food has been performed pursuant to Article 11 of the Food Safety Basic Law include the following:

- (i) A substance for which the establishment of an acceptable daily intake (ADI) was considered unnecessary: astaxanthin
- (ii) Substances whose potential to influence human health through food was considered negligible as far as used properly:

Inactivated vaccines including Bovine Mannheimia haemolytica inactivated vaccine and yellowtail infection mixed inactivated vaccine; and infectious bronchitis live vaccine

III. Treatment of exempted substances in other countries

(1) Codex standards with respect to the residues of veterinary drugs

- (i) Procedures For Recommending Maximum Residue Limits Residues Of Veterinary Drugs In Food (1987-1999), Joint FAO/WHO Expert Committee on Food Additives (JECFA), Rome 2000

7. Maximum Residue Limits (MRLs)

A. End point assessment

(Omitted)

When the Committee has determined that an ADI is unnecessary because the compound of interest is produced endogenously in humans and animals or for other valid toxicological considerations, then the Committee recommendation of an MRL is also deemed unnecessary. When an ADI is not allocated because the safety of the compound on toxicological considerations cannot be assured, then an MRL should not be recommended.

(Omitted)

(ii) Examples of substances for which an MRL is deemed unnecessary by the Codex

- a) Estradiol-17 β (bovine)
- b) Progesterone (bovine)
- c) Testosterone (bovine)
- d) PST (porcine somatotropin) (swine)

(2) Treatment in the U.S.

(i) Provisions allowing for exemption from the requirement of a residue standard for agricultural chemical residues in the U.S.

In the United States, provisions have been established for agricultural chemicals generally recognized as safe as well as provisions that allow for exemption from the requirement of a residue standard.

40 CFR Chapter 1 (Title 40, Chapter 1 of the Code of Federal Regulations)

Sections 180.2 Agricultural chemical chemicals considered safe.

- (a) As a general rule, agricultural chemical chemicals other than benzaldehyde (when used as a bee repellent in the harvesting of honey), ferrous sulfate, lime, lime-sulfur, potassium sorbate, sodium carbonate, sodium hypochlorite, sulfur, when used as plant desiccants sodium metasilicate (not to exceed 4 percent by weight in aqueous solution), and when used as postharvest fungicide oil of lemon, and oil of orange are not generally recognized as safe.

Subpart C Provisions allowing for exemption from the requirement of a residue standard

Sections 180.950 Exemptions for minimal risk ingredients.

Unless specifically excluded, residues resulting from the use of the following substances are exempted from the requirement of a residue standard, if such use is in accordance with GAP or GMP.

(a) Commonly consumed food commodities.

Commonly consumed food commodities means foods that are commonly consumed for their nutrient properties. The term commonly consumed food commodities shall only apply to food commodities in the form the commodity is sold or distributed to the public for consumption.

- (1) Included within the term commonly consumed food commodities are:
(i) sugars; (ii) spices; and (iii) herbs.
- (2) Excluded from the term commonly consumed food commodities are:
(i) any food commodity that is adulterated; (ii) both the raw and processed forms of peanuts, tree nuts, milk, soybeans, eggs, fish, crustacea, and wheat; (iii) alcoholic beverages; and (iv) dietary supplements.

(b) Animal feed items: Meat meal and field crops (excluding peanuts, etc.). Including hulls and shells of peanuts, etc.

(c) Edible fats and oils: Excluding oils used in the agricultural chemical formulation to impart their characteristic fragrance and/or flavoring.

(d) Specific chemical substances: Residues resulting from the use of the following substances are exempted from the requirement of a residue standard:

Excerpts: Acetic acid, cellulose, dextrans, lactic acid, lecithins, silica, potassium chloride, sodium chloride, urea, etc.

Sections 180.960 Polymers; exemptions from the requirement of a tolerance.

Residues resulting from the use of the following substances (those that meet the definition of a polymer and the criteria specified for defining a low-risk polymer) as ingredients in an agricultural chemical formulation, are exempted from the requirement of a residue standard.

Excerpts: Acetic acid ethenyl ester, etc.

Sections 180.1001 Exemptions from the requirement of a residue standard.

- (a) An exemption from a residue standard shall be granted when it appears that the total quantity of the agricultural chemical in or on all raw agricultural commodities for which it is used will involve no hazard to the public health.
- (b) When applied to growing crops, in accordance with GAP, the following agricultural chemical chemicals are exempt from the requirement of a residue standard (except when applied to a crop at the time of or after

harvest):

- (1) [Reserved]
- (2) N-Octylbicyclo(2,2,1)-5-heptene-2,3-dicarboximide
- (3) Petroleum oils
- (4) Piperonyl butoxide
- (5) [Reserved]
- (6) Pyrethrum and pyrethrins
- (7) Rotenone or dorriss or cube roots
- (8) Sabadilla

- (c) Residues of the following materials are exempted from the requirement of a residue standard when used in accordance with GAP as ingredients in agricultural chemical formulations applied to growing crops or to raw agricultural commodities after harvest:

Excerpts: Approximately 500 materials, including acetic acid, acetone, ammonium chloride, benzoic acid, and activated carbon.

- (d) The following materials are exempted from the requirement of a residue standard when used in accordance with GAP as ingredients in agricultural chemical formulations applied to growing crops only:

Excerpts: Approximately 500 materials, including acetonitrile, animal waste material, carrageenan, diethylene glycol.

- (e) The following materials are exempted from the requirement of a residue standard when used in accordance with GAP as ingredients in agricultural chemical formulations applied to animals:

Excerpts: Approximately 400 materials, including acetic acid and ethyl alcohol

Sections 180.1002 – 1241 Individual materials exempted from the requirement of a residue standard

(An exemption from a residue standard is granted separately for different materials when applied to specific crops.)

- (ii) Provisions allowing for exemption from the requirement of a residue standard for animal drug residues in the U.S.

CFR 21.556 (Title 21, Section 556 of the Code of Federal Regulations)

General provisions; tolerance for residues of new animal drugs in food

- (a) Tolerances established in this part are based upon residues of drugs in edible products of food-producing animals treated with such drugs. Consideration of an appropriate tolerance for a drug shall result in a conclusion either that:

(Omitted)

- (4) It may or may not be possible to determine whether residues will be incurred but there is no reasonable expectation that they may be present, in which case the establishment of a tolerance is not required.
- (5) The drug is such that it may be metabolized and/or assimilated in such form that any possible residue would be indistinguishable from normal tissue constituents, in which case the establishment of a tolerance is not required.

Examples of substances for which no MRLs are considered necessary in CFR 21.556

- a) Colistimethate (unnecessary for chicken)
- b) Lincomycin (unnecessary for chicken; for swine there is an MRL)
- c) Trenbolone

(3) Provisions allowing for exemption from the requirement of a residue standard for animal drug residues in the EU

- (i) EEC No.2377/90 Regulation on the establishment of MRL of veterinary medicinal products in foodstuffs of animal origin

Article 3

Where, following an evaluation of a pharmacologically active substance used in veterinary medicinal products, it appears that it is not necessary for the protection of public health to establish a MRL, that substance shall be included in a list of Annex II, which shall be adopted in accordance with the procedure laid down in Article 8.

“Notice to applicants and note for guidance, Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin, September 2001”

Part II- Notice to applicants for the establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin by the European Union in accordance with Council Regulation (EEC) No.2377/90

I. Purpose and scope of Council Regulation (EEC) No.2377/90

3. Types of MRLs and other outcomes of evaluation (excerpts)

Council Regulation (EEC) No.2377/90 envisages that at the end of an evaluation a substance may be inserted into one of four Annexes, three of which allow the use of the substance in food-producing animals.

(Omitted)

Annex II contains the list of substances for which no MRLs are necessary because, at the time the evaluation was completed, residues of the substance concerned were not considered to present a public health risk. It should be noted that a substance may be proposed for insertion into Annex II only after the evaluation of the safety of residues of the substance concerned. Thus a decision to insert a substance in Annex II has the same effect as the allocation of MRLs to a substance in Annex I. For this reason the expression “the establishment of MRLs” is used to cover the inclusion of a substance in Annex II. A recommendation to insert a substance in Annex II should not be interpreted as automatically implying that no withdrawal period is necessary. At the present time, decisions concerning withdrawal periods are taken on a case by case basis either by the Member States, or by the Commission in relation to centrally approved marketing authorisations.

(ii) Substances for which no MRLs are considered necessary in EEC No.2377/90

As shown below, MRLs are considered unnecessary for 508 substances, for 214 of which limitation has been established on animals involved and/or applications methods.

- a) Inorganic compounds: e.g. Aluminium hydroxide acetate, aluminium phosphate
- b) Organic compounds: e.g. Estradiol-17 β , 1-methyl-2-pyrrolidone
- c) Substances generally recognized as safe: e.g. Absinthium extract, acetylmethionine
- d) Substances used as homeopathy medicines: e.g. *Adonis vernalis*, *Aesculus hippocastanum*
- e) Substances used as food additives: e.g. Substances with E-numbers
- f) Substances of plant origin: e.g. *Aloe vera*, *Angelicae radix aetheroleum*, *Anisi stellati fructus*

(4) Provisions allowing for exemption from the requirement of a residue standard for residues of agricultural chemicals and animal drugs in Australia

(i) Australian Pesticides and Veterinary Medicines Authority

Maximum residue limits in food and animal feedstuff (June 2004)

Table 5 Uses of substances where maximum residue limits are not necessary

- a) When no residues occur or are expected to occur in food or animal feedstuff

- b) When it is impossible to distinguish the residue from substances naturally occurring in food
 - c) When the residue is toxicologically insignificant
- (ii) Examples of substances for which no MRLs are considered necessary in Australia
- a) Metalaxyl (when used for seed dressing)
 - b) Lindane (when used for seed dressing)
 - c) Progesterone (when used as an estrus synchronizer)

IV. Regarding the establishment of exempted substances (draft)

Regarding the establishment of the “substances to be determined by the Minister of Health, Labour and Welfare as those that apparently have no potential to cause damage to human health” as Specified in Article 11, Paragraph 3 of the Food Sanitation Law (exempted substances), possible ideas can be summarized as follows:

- (1) Appropriate substances to be designated as exempted substances are, among substances used as agricultural chemicals, etc., those for which any agricultural, livestock or aquatic products in which residues of the substance concerned occur apparently have no potential to cause damage to human health, considering the condition and extent of such residues.
- (2) In addition to the specified agricultural chemicals as stipulated in the Japanese Agricultural Chemicals Regulation Law, appropriate substances to be designated as exempted substances include, among the agricultural chemicals for which no standard for withholding of registration have been established, those for which the ingestion of crops produced using the agricultural chemical concerned has no potential to cause immediate damage to human health.
- (3) Some of the substances for which the establishment of residue standards is considered unnecessary in other countries are subject to limitation on animals involved and/or applications methods. However, as it is difficult to establish limitation on usage, etc. for exempted substances in question, only the agricultural chemicals, etc. for which no limitation on usage, etc. is established (among substances for which the establishment of residue standards is considered unnecessary) should be exempted substances to be subject to a positive list system.
- (4) Agricultural chemicals, etc. for which the establishment of residue standards is considered unnecessary due to their usage, etc. will be revised after the implementation of a positive list system, considering results of investigations such as a survey of daily intakes.

V. Draft List of Exempted Substances

Note: the underlined part will be officially published.

- When a health impact assessment of food has been performed pursuant to Article 11 of the Food Safety Basic Law
 - (i) A substance for which the establishment of an acceptable daily intake (ADI) was considered unnecessary: astaxanthin
 - (ii) Substances whose potential to influence human health through food was considered negligible as far as used properly:

Inactivated vaccines including Bovine Mannhemia haemolytica inactivated vaccine and yellowtail infection mixed inactivated vaccine; and infectious bronchitis live vaccine
- Specified Agricultural Chemicals
- Foods

(Insecticides) fatty acid-glycerid, starch, hidroxypropyl starch, rapeseed oil
(Biocides) extract from SHITAKE mushroom
(Plant Growth Regulators) extract from chlollera
(Others) lemon oil, orange oil, sugars, spices, herbs, edible oil, lactic acid, urea, etc.
(Animal Drugs) red pepper, laurel leaf
- Food Additives and other chemicals

(Insecticides) oleate, propylenglycol-*m*-fatty acid-ester, diatomaceous earth, carbon dioxide, lecithin, machine oil
(Adhering agents) paraffin, wax
(Others) choline chloride, slaked lime, iron sulfate, hypochlorite, sorbic acid, meta-silicate
(Animal Drugs) vitamins (excluding beat-carotin), aminoacid
- Others
ammonium sulfate, caffeine, theobromine, papain, betain (trymethylglycine), lanoline, trypsin, pepsin
- Microbial Pest Control Products
- Natural Enemies

In the cases for minerals such as copper and sulfur, the paragraph 4 of the General Provision to Enforce the Positive List System is applied. The paragraph says “For substances that are not listed in the table given in the previous section and that may remain in foods as environmental contaminants, concentrations in the foods shall not exceed levels that are normally included in the foods.”