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## Japan

### Sanitary/Phytosanitary/Food Safety

#### Proposed Changes to Standards on Metconazole; Cyazofamid; Enrofloxacin; and Regulations on e. coli levels in certain wheat products.

**2006**

**Approved by:**

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**Report Highlights:**

On June 15 the Japanese Ministry of Health, Labour and Welfare (MHLW) informed Tokyo based Embassies of its intention to Establish new MRLs for the pesticides Metconazole and Cyazofamid, to establish MRLs for the veterinary drug Enrofloxacin, and to partially revise the Official Specifications and Standards for e. coli in certain wheat based products. These changes are currently open for public comments until June 29, 2006. Sometime after comments are received, a final draft will be submitted to the WTO for an additional public comment period.

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Includes PSD Changes: No  
Includes Trade Matrix: No  
Unscheduled Report  
Tokyo [JA1]  
[JA]

## (I) Establishment of Maximum Residue Limits for Metconazole and Cyazofamid, Pesticides, in Food

### Purpose

This activity is to develop specifications and standards for foods. Under the provisions of Article 11, Paragraph 1 of the Food Sanitation Law, the Minister of Health, Labour, and Welfare may establish maximum residue limits (MRLs) for agricultural chemicals that may remain in foods. Any food for which standards are established pursuant to the provisions, is not permitted to be marketed unless such food complies with the established standards.

On November 29, 2005 the Ministry of Health, Labour and Welfare issued notifications regarding the positive list system for agricultural chemicals in food (Notification Nos. 497, 498, and 499). Under the system, which became effective on May 29, 2006, basically, any agricultural chemical in food in the Japanese marketplace is subject to residue standards based on the law.

### Outline of the activity

Metconazole (Fungicide): This chemical is currently not permitted for use in Japan. This proposal is to newly approve it under the Agricultural Chemicals Regulation Law. In step with approval, the MHLW will establish new MRLs. See the list of draft MRLs (Attachment 1).

Cyazofamid (Fungicide): This chemical is already approved. The scope of target crops on which it is permitted for use will be expanded. In step with the expansion of scope, the MHLW will additionally establish MRLs for some crops. In addition, some of the provisional MRLs, which have been set in Notification No. 499, will be revised based on scientific data. See the list of draft MRLs (Attachment 2).

Revised provisional MRLs will be removed from the provisional MRLs list in the Specifications and Standards for Food, Food Additives, Etc (Part I Food, Section A General Compositional Standards for Food, Item 7) and placed in the MRLs list (Item 6 of Section A).

### Attachment 1. draft changes Metconazole (Fungicide)

<u>Commodity</u>	<u>draft MRL (ppm)</u>
Wheat	0.2
UNSHU orange	0.1
NATSUDAIDAI (whole)	0.2
Lemon	0.3
Orange (including Navel)	0.3
Grapefruit	0.3
Lime	0.3
Other citrus fruits	0.3
UNSHU orange (peel)	3

Attachment 2.  
Cyazofamid (Fungicide)

<u>Commodity</u>	<u>Current MRL</u>	<u>Draft MRL (ppm)</u>
Wheat	0.05	0.05
Beans (dry)	0.1	
Potato	0.05	0.05
Taro	0.02	
Japanese radish (root)	0.05	
Japanese radish (leaf)	10	
Turnip (including Rutabaga)(root)	0.3	
Turnip (including Rutabaga)(leaf)	20	
Chinese cabbage	1	0.7
Cabbage	0.05	0.05
Kale	15	
KOMATSUNA	15	15
KYONA 10		
Qing-geng-cai	3	
Broccoli	1	
Other cruciferous vegetables	15	
Onion	0.05	0.05
Welsh (including Leek)	2	
Other liliaceous vegetables	3	
Tomato	2	2
Pimento (Sweet pepper)	1	1
Eggplant	0.5	2
Other solanaceous vegetables	1	1
Cucumber (including Gherkin)	0.7	0.7
Pumpkin (including Squash)	0.1	2
Oriental pickling melon (vegetable)	0.1	2
Water melon	0.05	0.05
Melons	0.05	0.05
MAKUWAURI	0.1	0.1
Other cucurbitaceous vegetables	0.1	0.1
Spinach	25	25
Ginger	0.7	
UNSHU orange	0.7	
NATSUDAIDAI (whole)	2	
Lemon	5	
Orange (including Navel)	5	
Grapefruit	5	
Lime	5	
Other citrus fruits	5	
Strawberry	0.7	
Grape	10	10
Other fruits	1	10
UNSHU orange (peel)	10	
Other spices (except UNSHU peel)	1	10
Other herbs	15	

## (II) Discussion on the Establishment of Standards for Enrofloxacin, Veterinary Drug, in Food

(Summary)

### I Background

This activity is to establish standards for enrofloxacin, an antibiotic. Enrofloxacin is the major effective ingredient of certain veterinary medicines (Baytril raw materials, Baytril 10% solution, Baytril 2.5% HV solution, and Baytril 2.5%, 5%, and 10% injectable solutions) which are approved under the Pharmaceutical Affairs Law. For this substance, residue standards for food (provisional MRLs) are already established. This time, an application has been made to MAFF for reassessment of these drugs based on the legal requirement, under which reassessment must be conducted every six years after veterinary drugs are once approved. In step with reassessment, the MHLW is going to review the provisional MRLs as the Food Safety Commission in the Cabinet Office has set the acceptable daily intake (ADI) of this substance.\*

Note: Under the 2003 amendment of the Food Sanitation Law, when an application is made to MAFF for the approval of an agricultural chemical, the MHLW is required to establish MRLs for the chemical. Provisional MRLs are MRLs which have been provisionally established for the implementation of the positive list system for agricultural chemical residues in food, which became effective on May 29, 2006.

### II Summary report of discussion at the Joint Committee on Agricultural Chemicals and Veterinary Drug under the Pharmaceutical Affairs and Food Sanitation Council

#### 1. Substance Enrofloxacin

Chemical name: 1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid

2. Use (treatment of bacterial infections of the respiratory and alimentary tract)  
It is categorized as a fluoroquinolone and effective against gram-negative bacteria as well as various gram-positive bacteria. In Japan, it is used to treat bacterial respiratory infections (*Mycoplasma bovis*, *Ureaplasma divesum*, *Pasteurella multocida*) and coliform-bacterial diarrhea of cattle and pigs, and respiratory mycoplasma infections (*Mycoplasma gallisepticum*) and coliform-bacterial infections of chickens. Ciprofloxacin, a metabolite of enrofloxacin, has anti-bacterial activity and widely used in human medicine.

#### 3. Acceptable daily intake (ADI)

According to risk assessment by the Food Safety Commission, NOAEL (No Observed Adverse Effect Level) for two-year chronic toxicity study in rats was 2.9 mg/kg body weight. The ADI was derived as 0.029 mg/kg body weight/day, applying a safety factor of 100, which consists of two 10-fold factors for interspecies differences and for interindividual variability in humans. On the other hand, the ADI derived from microbiological effects based on in vitro MIC50 values was 0.002 mg/kg body weight/day, applying a faecal bolus of 220 g, 20% for the quantity of the ingested amount which would be available to the bacteria at the distal part of the intestine, and a body weight of 60 kg.

$$\text{ADI (mg/kg bw/day)} = \frac{0.000125(\text{mg/ mL}) \times 220 \text{ g}}{0.2 \times 60(\text{kg})} = 0.002 \text{ mg / kg bw / day}$$

\* The value is based on findings in humans of the metabolite, ciprofloxacin. In the comparison of the two ADIs, the microbiological ADI is lower than the toxicological ADI.

The commission has adopted the stricter one and established an ADI of 0.002 mg/kg body weight for enrofloxacin.

The assessment report from the commission is available (Japanese only) at <http://www.fsc.go.jp/hyouka/hy/hy-hyouka-enrofloxacin.pdf>

#### 4. Regulatory status in other countries

Enrofloxacin is permitted for use in food producing animals, such as cattle and pigs, in many countries. MRLs are established in each country. See the table given below. On September 12, 2005 the United States withdrew the approval of the use of this substance in chickens, based on risk assessment of enrofloxacin-resistant campylobacter. In the EU, MRLs are set for all food producing animals, but the use in cultured aquatic animals is not approved. The JECFA (Joint FAO/WHO Expert Committee on Food Additives) has assessed the safety of the substance and established an ADI of 0.002 mg/kg body weight/day.

MRLs by countries (Unit: ppm)

Target tissue	USA	EU <sup>(3)</sup>	Canada	Japan <sup>(5)</sup>
<b>Cattle</b>				
Muscle		0.1	0.02	0.01
Fat		0.1		0.01
Liver	0.1	0.3	0.07	0.01
Kidney		0.2		0.01
Other edible parts <sup>(1)</sup>				0.01
Milk		0.1		0.02
<b>Porcine</b>				
Muscle		0.1		0.01
Fat		0.1		0.01
Liver		0.2		0.01
Kidney		0.3		0.01
Other edible parts				0.01
<b>Other terrestrial mammals</b>				
Muscle		0.1		0.1
Fat		0.1		0.1
Liver		0.3		0.3
Kidney		0.2		0.2
Other edible parts				0.2
<b>Chicken</b>				
Muscle		0.1		0.01
Fat		0.1		0.01
Liver		0.2		0.01
Kidney		0.3		0.01
Other edible parts				0.01
<b>Other fowls</b>				
Muscle		0.1		0.1
Fat		0.1		0.1
Liver		0.2		0.2
Kidney		0.3		0.3
Other edible parts				0.2
Fin fish and shellfish <sup>(2)</sup>		0.1 <sup>(4)</sup>		0.1

## Note

1. "Other edible parts" refer to all edible parts except the muscle, fat, liver, and kidney.
2. "Fin fish and shellfish" refer to all edible fin fish and shellfish
3. The limits of the EU are expressed as the sum of residue levels of enrofloxacin and ciprofloxacin.
4. A MRL of 0.1 applies the MRL for the muscle for all food producing species except cattle, sheep, pigs, goats, rabbits, and poultry.
5. The Japanese MRLs are provisional MRLs specified in the Minister of Health, Labour and Welfare Notification No. 499, published in November 29, 2005 and implemented on May 29, 2006.

## 5. Draft maximum residue limits (MRLs)

a. Target substances to regulate  
Enrofloxacin and Ciprofloxacin

b. The table shows draft MRLs. The MRLs were established taking residue studies into consideration. Japan will not establish MRLs for fin fish and shellfish since most foreign countries do not approve the use of enrofloxacin in such animals and there occur no residue studies for cultured aquatic animals. The MHLW will review the MRLs given below when the commission has completed assessment of effects of bacterial resistance to enrofloxacin and ciprofloxacin.

Tissue (animal species)	MRL (ppm) <sup>2</sup>	Tissue (animal species)	MRL (ppm) <sup>2</sup>
Cattle		Chicken	
Muscle	0.05	Muscle	0.05
Fat	0.05	Fat	0.05
Liver	0.1	Liver	0.1
Kidney	0.1	Kidney	0.1
Other edible parts <sup>1</sup>	0.05	Other edible parts <sup>1</sup>	0.1
Milk	0.05		
Porcine		Other fowls	
Muscle	0.05	Muscle	0.05
Fat	0.05	Fat	0.05
Liver	0.1	Liver	0.1
Kidney	0.1	Kidney	0.1
Other edible parts <sup>1</sup>	0.05	Other edible parts <sup>1</sup>	0.1
Other terrestrial mammals			
Muscle	0.05		
Fat	0.05		
Liver	0.1		
Kidney	0.1		
Other edible parts <sup>1</sup>	0.05		

## Note

1. For other edible parts, MRLs were based on residue study results of the small intestine for cattle and pigs, and on residue study results of the liver and kidney for chickens.
2. MRLs are expressed as the sum of residue levels of enrofloxacin and ciprofloxacin.

## c. Ratio of ADI

The table shows the ratios of the TMDI (theoretical maximum daily intake) to the ADI. The TMDI refers to the amount of enrofloxacin that is estimated to be consumed a day, based on the National Nutrition Survey, when it is assumed that the substance remains in each food up

to the draft maximum residue limit. The details of the estimation are shown in the table given in the last page of this document.

## TMDI/ADI (%)

National average	10.41
Young children, aged between 1 and 6	41.40
Pregnant women	11.83

d. MRLs for enrofloxacin are already established in the revised Specifications and Standards for Food, Food Additives, Etc (Part I Food, Section A General Compositional Standards for Food, Item 7). These MRLs have, however, been provisionally established for the implementation of the positive list system for agricultural chemical residues in food, which became effective on May 29, 2006. In this activity, the MHLW has revised the provisional MRLs based on more appropriate and scientific assessment. The provisional MRLs will be removed from Item 7, and the revised MRLs will be placed in Item 6 of Section A.

Estimation of ratio of ADI (Based on the national average intake of each food and a body weight of 53.3 kg)

## Note

1. [MRL for muscle] × [Sum of intakes of muscle and fat]
2. The highest MRL in the same species was adopted for calculation.

<u>Food</u>	<u>MRL (ppm)(A)</u>	<u>Intake(g/person/day)(B)</u>	<u>Estimated intake of enrofloxacin (µg/person/day) (A) × (B)</u>
Cattle			
Muscle	0.05	19.71	0.986 <sup>1</sup>
Fat	0.05	19.71	0.986 <sup>1</sup>
Liver	0.1	0.12	0.012
Kidney	0.1	0.4	0.04
Other edible parts <sup>1</sup>	0.05	0.42	0.021
Milk	0.05	142.7	7.14
Porcine			
Muscle	0.05	35.83	1.792 <sup>1</sup>
Fat	0.05	35.83	1.792 <sup>1</sup>
Liver	0.1	0.17	0.017
Kidney	0.1	0.04	0.004
Other edible parts <sup>1</sup>	0.05	0.39	0.020
Other terrestrial mammals			
Muscle	0.05	0.33	0.033 <sup>2</sup>
Fat	0.05	0.33	0.033 <sup>2</sup>
Liver	0.1	0.33	0.033 <sup>2</sup>
Kidney	0.1	0.33	0.033 <sup>2</sup>
Other edible parts <sup>1</sup>	0.05	0.33	0.033 <sup>2</sup>
Chicken			
Muscle	0.05	19.76	0.988 <sup>1</sup>
Fat	0.05	19.76	0.988 <sup>1</sup>
Liver	0.1	0.29	0.029
Kidney	0.1	0	0
Other edible parts <sup>1</sup>	0.1	0.15	0.015

<u>Food</u>	<u>MRL (ppm)(A)</u>	<u>Intake(g/person/day)(B)</u>	<u>Estimated intake of enrofloxacin (µg/person/day) (A) × (B)</u>	
Other fowls				
Muscle	0.05	0.11	0.011 <sup>2</sup>	
Fat	0.05	0.11	0.011 <sup>2</sup>	
Liver	0.1	0.11	0.011 <sup>2</sup>	
Kidney	0.1	0.11	0.011 <sup>2</sup>	
Other edible parts <sup>1</sup>	0.1	0.11	0.011 <sup>2</sup>	
			Total (µg/person/day)	11.10
			Acceptable Daily Intake (µg/person/day)	106.6
			TMDI/ADI (%)	10.41

### (III) Discussion on the Partial Revision of Specifications and Standards for Frozen Foods Served after Heating

(Summary)

#### I Background

Frozen bread dough and its variations whose main ingredient is wheat flour are categorized as “frozen foods served (excluding products which are heated before they are frozen)” in the specifications and standards for food and food additives based on the Japanese Food Sanitation Law. The law requires all the foods categorized in this food group to test negative for E.coli. Some reports reveal that wheat flour may be contaminated with E.coli. It is very difficult to keep these products free from E. coli contamination because complete bacterial killing is technically impossible in the production course without any preheating treatment before freezing process. The Ministry of Health, Labour and Welfare (MHLW) has determined that the application of the E. coli requirement to the frozen wheat flour dough products is not practicable and asked the Food Safety Committee (FSC) to conduct risk assessment.

In April 2006, the FSC made the conclusion: For frozen bread dough and its variations whose main ingredient is wheat flour and which require heating treatment before consumption, the abolishment of the requirement (negative for E. coli) is unlikely to lead to an increase in health risks as long as they are sufficiently heated or baked before consumption. In response to the conclusion, the MHLW will revise the specifications and standards for the frozen foods served after heating (excluding products which are heated before they are frozen).

#### II A Summary Report of Discussion at the Committee on Food Standards under the Pharmaceutical Affairs and Food Sanitation Council

1. Definition of frozen bread dough and its variations whose main ingredient is wheat flour and which require heating treatment before consumption “Frozen bread dough and its variations whose main ingredient is wheat flour” are defined as frozen foods served after heating (excluding products which are heated before they are frozen) whose main ingredient is wheat flour and which are needed to be heated at high temperature before consumption. They are represented by frozen bread dough and include:

- (1) Frozen bread dough (dough for all kinds of breads, including pastry and other bakery products, including donuts and pies)
- (2) Frozen pizza dough
- (3) Frozen bread dough containing fillings, such as jams and sweetened red-bean-paste

## 2. Definition of E.coli specified by the Food Sanitary Law

The law specifies the E.coli requirement for frozen foods as an indicator of fecal contamination. The law considers E. coli as the coliform bacteria which show the pattern [++-] when the IMViC tests are conducted according to the specified procedure, and they are different from Escherichia coli based on the taxonomic category or bacteria called coliform bacteria in other countries.

### Definition of E.coli specified by the Food Sanitary Law

E. coli are bacteria which generate gas when incubated in an EC fermentation vial at  $44.5 \pm 0.2^\circ\text{C}$  for  $24 \pm 2$  hours and which are confirmed as coliforms, or fecal coliforms, based on the coliforms test.

## 3. Revision of the specifications and standards for foods and food additives

In response to the conclusion by the FSC, the Committee on Food Standards has determined that the E. coli requirement is not needed to apply to “frozen bread dough and its variations whose main ingredient is wheat flour and which require heating process before consumption.” The existing specifications and standards should be partially revised.

In addition, the MHLW should direct the manufacturers of these dough products to voluntarily conduct hygiene management for the products according to good manufacturing practice. The MHLW should also direct them to give written information (e.g., label information and insertions) to end users of these products (e.g., bakeries and general consumers) to ensure that the final products are free of E. coli. The information includes the excluding products which are heated before they are frozen or baking and other necessary instructions.

### **Please send comments directly to:**

Standards and Evaluation Division, Department of Food Safety,  
Pharmaceutical and Food Safety Bureau,  
Ministry of Health, Labour and Welfare  
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Please also consider sending a copy of your comments to USDA’s Foreign Agricultural Service, well before the deadline, for possible inclusion into official U.S. Government comments:

Food Safety and Technical Services  
International Trade Policy Division  
USDA Foreign Agricultural Service  
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