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Research report

Research on the safety evaluation of existing additives

FY 1999

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This document is the English translation of "*既存添加物の安全性評価に関する調査研究（平成11年度調査）*" as a service to a broad international audience/readers. This English version is provided for reference purposes only. In the event of any inconsistency between the Japanese original and English translation, the former shall prevail.

Administrative Information, Ministry of Health, Labour and Welfare

December 14, 2000: Data relating to press release
Research on the safety evaluation of existing additives (FY 1999 Survey)

Research on the safety evaluation of existing additives

(December 14, 2000: Released by the Food Chemistry Division, Environmental Health Bureau, Ministry of Health and Welfare)

The Ministry of Health and Welfare released the FY 1999 survey results of "Research on the safety evaluation of existing additives."

Released text

FY 1999 food additive safety evaluation, etc., grant research
Food additive safety evaluation grant research

Research report

Research on the safety evaluation of existing additives

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Summary

In the FY 1996 health and welfare science grant research report, "Research on the safety evaluation of existing additives" (Senior Researcher: Hayashi Yuzo) (hereinafter referred as "Hayashi Group Report") which reviewed existing additives based on international evaluation results, approval status in Europe and the United States, available safety study results, etc., it

was concluded that 139 out of 489 additives should be evaluated by the additional safety results including the newly performed studies in the future..

In this study, an investigation was performed on food additives for which safety study results were newly available among the 139 additives that were considered to require further investigation regarding safety in the Hayashi Group Report. In FY 1998, 9 additives were investigated, namely: Carob germ colour, Licorice oil extract, Enzymatically modified isoquercitrin, Tamarind colour, Xanthomonas campestris protein, Phaffia colour, Pecan nut colour, Mousouchiku extract, and Levan. In addition, in FY 1999, 5 additives were investigated, namely: Itaconic acid, Orange colour, Chitin, Milt protein, and Haematococcus algae colour. This report collectively lists the investigation results for these 14 additives.

The results of a 28-day or longer repeated dose study and a mutagenicity study were available for each of the 14 investigated additives, and basic safety, as a substance could be evaluated for each, based on the study results. As there is presently no study result that suggests any immediate effects on human health, it is considered that there is no immediate need to perform a new safety study.

A. Objective

Due to the amendment of the Food Sanitation Act in May 1995, the designated system of food additives, previously targeted only chemically synthesized additives, expanded into all additives except for natural flavors, etc. Upon this amendment, the additives except those that are chemically synthesized (excluding natural flavors, etc.; hereinafter, referred to as “natural additives”) which already have been distributed, manufactured, used, were defined by the list of existing additives, and were then permitted the continuation of sales, manufacture, import, etc., as a transitional measure.

However, unlike additives that have been previously designated, the natural additives on the list of existing additives have not been checked individually for safety, therefore, confirmation of their safety is requested in the Diet, etc.
In FY 1996, the basic safety of 489 existing additives was investigated based on international evaluation results, approval status in Europe and the United States, and safety study results, etc., and was then published as the Hayashi Group Report. In the report, it is stated that “Of the 489 additives, 159 have already been evaluated internationally and their basic safety has been confirmed. In addition, it was considered that there is no urgent need to investigate the safety of 41 additives based on the evaluation of available test results and 150 additives based on their origin, method of preparation and definition, at the present stage.” Therefore, the report concluded that the remaining 139 additives are still required further investigation.
The present survey aimed to investigate the basic safety of natural additives by collecting domestic and overseas study results and evaluating those results in 139 additives that had been considered to require investigation for safety in the FY 1996 Hayashi Group Report.

B. Methods

Among the 139 existing additives that were considered to require an investigation for safety in the Hayashi Group Report, additives for which the results of both a 28-day or longer repeated-dose toxicity study results and a mutagenicity study available were individually subjected to an evaluation of those safety study results. Additives which had been newly evaluated after the point of survey in the Hayashi Group Report were also reviewed in the Joint FAO/WHO Expert

Committee on Food Additives (hereinafter referred to as "JECFA") and other countries, etc.

C. Results

(1) Collection and evaluation of safety study results

Among the 139 existing additives that were considered to require an investigation for safety, there were 14 additives for which the results of both a 28-day or longer repeated-dose toxicity study results and a mutagenicity study were available.

The safety of these additives was investigated by individually evaluating the study results, and there is no study result that suggests any immediate effects on human health, at present, for any of these 14 additives. A summary of the results is shown in Annex 1.

(2) Safety evaluation status by the JECFA (Table 1)

Summarizing the evaluation results by the JECFA for 489 additives that were listed in the list of existing additives, a total of 78 additives have been evaluated, including: 14 additives for which the acceptable daily intake (hereinafter, referred to as the "ADI") has been set; 47 additives for which the establishment of the ADI was toxicologically considered unnecessary (ADI not specified or not limited); 5 additives for which the ADI has been provisionally established; and, 12 additives for which the ADI has not been established, but the current use of which is judged to present no toxicological problems (GMP (no problem as long as properly used in food production), acceptable (acceptable under the current conditions for use)).

(3) Authorization status in the United States or the EU (Table 1)

137 additives were authorized as additives for distribution or designated as GRAS (Generally recognized as Safe) substances in the United States, while 55 additives were authorized as additives for distribution in the EU.

The current safety evaluation for 489 existing additives is summarized, as shown in Table 2, based on the Hayashi Group Report, the present survey results, and the evaluation status in the United States and the EU.

D. Discussion

Safety study results were collected for the 139 existing additives that had been considered to require an investigation for safety, and the study results were evaluated for 14 existing additives for which the results of both a day or 28-day repeated-dose toxicity study and a mutagenicity study were available. A summary of the results is presented in Annex 1. As there were no study results that suggest any immediate effects on human health at present for any of these additives, it is therefore considered that there is no immediate need to perform a new safety study for the 14 existing additives that were evaluated.

Regarding evaluation by international organizations, etc., 4 additives, namely: α-Acetolactate decarboxylase, Curdlan, Caramel II, and Trehalose were newly evaluated by the JECFA after the Hayashi Group Report, and the ADI was established or considered unnecessary (Table 1). Among these additives, Curdlan and Caramel II have already been approved for use in the

United States and/or the EU, and the Hayashi Group Report indicated that there is no immediate need to perform a safety study for the other 2 additives based on their origin, method of preparation, and definition. Three additives, namely: Invertase, β-Cyclodextrin, and Microcrystalline wax were newly evaluated in the EU (Table 2). Among these additives, Microcrystalline wax and β-Cyclodextrin are additives that have already been evaluated by the JECFA, and the Hayashi Group Report indicated that there is no immediate need to perform a safety study for Invertase because it is an enzyme. Therefore, none of the additives that were evaluated by international organizations, etc. corresponded to the 139 additives that were reported to require an investigation of safety in the Hayashi Group Report.

Based on the above results, it is considered that there is a need to collect further information, including the implementation of a safety study, for 125 additives among the 139 existing additives that were considered to require a safety confirmation in the Hayashi Group Report (Table 3), excluding the 14 additives evaluated in the present survey.

In addition, among the additives described in Table 3, those that were not considered to be distributed in the survey in FY 1999 (Japan Food Additives Association) are also described in Table 3, for reference.

E. Conclusion

The basic safety of 14 existing additives was newly confirmed by this survey, based on the collected study results. It is considered that there is no immediate need to perform a safety study, at the present stage for any of these additives.

Table 1. Natural additives for which safety has been evaluated in foreign countries

Name in the list of existing additives	Evaluation by the JECFA (Note 1)			Status in the United States (Note 2)			Status in the EU (Note 3)	
	Name	ADI (mg/kg b.w.)		Name	FDA evaluation	FASEB evaluation	Name	SCF evaluation
L-Asparagine				L-Asparagine (172.320)		Available		
L-Aspartic acid				L-Aspartic acid (172.320)		Available		
α-Acetolactate decarboxylase	α-Acetolactate decarboxylase	Not specified	51					
Annatto extracts	Annatto extracts	0.065 (As bixin)	26	Annatto extract (73.30)			Annatto, bixin, norbixin (E160(b))	Available (79)
Aminopeptidase				Aminopeptidase, an enzyme preparation derived from lactococcus lactis (184.1985)	Available (96)			
α-Amylase	α-Amylase from Bac.subtilis, α-Amylase from Asp. oryzae, var.; etc.	Not specified Not specified	31 31	Carbohydrase and cellulase derived from Asp. niger (173.120) Rhizopus oryzae (173.130) α-Amylase enzyme preparation from Bac. stearothermophilus (184.1012)				
β-Amylase	Malt Carbohydrases	Not limited	15	Carbohydrase and cellulase derived from Asp. niger (173.120) Carbohydrase from Rhizopus oryzae				
L-Alanine				L-Alanine (172.320)		Available		
Gum arabic	Gum arabic (Acacia gum)	Not specified	35	Acacia (gum arabic) (184.1330)		Available (73)	Acacia gum (gum arabic)	Available (78)
L-Arginine				L-Arginine (172.320)		Available		
Alginic acid	Alginic acid	Not specified	39	Alginic acid (184.1011)		Available	Alginic acid (E400)	Available (78)
Aluminium	Aluminium	PTWI 7 (Provisional tolerable weekly intake)	33				Alminium (E173)	Available (75)
Iso-α-bitter acid				Hops/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)				
Inositol				Inositol (184.1370)		Available		
Sweet potato carotene	Carotene (vegetable)	Acceptable under current use conditions	41	β-Carotene (73.95)		Available (80)	Carotenes (E160(a))	
Invertase							Invertase (E1103)	Available (78)
Turmeric colour	Curcumin	1.0 (Provisional)	51	Turmeric oleoresin (73.615)			Curcumin (E100)	Available (75)
Urease				Urease (184.1924)	Available (92)			
Ozone				Ozone (184.1563)				

Name in the list of existing additives	Evaluation by the JECFA (Note 1)			Status in the United States (Note 2)			Status in the EU (Note 3)	
	Name	ADI (mg/kg b.w.)		Name	FDA evaluation	FASEB evaluation	Name	SCF evaluation
Oregano extract				Origanum/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)				
Kaolin	Aluminium silicate	Not specified	29	Kaolin (184.1256)		Available		
Catalase	Catalase from bovine liver	Not limited	15	Catalase (bovine liver) (184.1034, etc.)	Available (95)			
Active carbon	Activated carbon	Not limited	31					
Gum ghatti				Gum ghatti (184.1333)		Available		
Curdlan	Curdlan	Not specified	53	Curdlan (172.809)	Available (96)			
Caffeine (extract)				Caffeine (182.1180)		Available		
Carrageenan	Carrageenan Processed Euchema seaweed	Not specified (provisional) Not specified (provisional)	51 51	Carrageenan (172.620)		Available (73)	Carrageenan (E407) Processed euchema seaweed (E407a)	Available (78)
α-Galactosidase				α-Galactosidase (173.145)				
β-Galactosidase				Lactase enzyme preparation from Kluyveromyces lactis (184.1388) Lactase enzyme preparation from Candida pseudotropicalis (184.1387)				
Mustard extract				Mustard/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)		Available (75)		
Caramel I	Caramel color I	Not specified	29	Caramel (73.85)		Available	Plain caramel (E150(a))	Available (89)
Caramel II	Caramel color II	160	55	Caramel (73.85)		Available	Caustic caramel (E150(b))	Available (89)
Caramel III	Caramel color III	200 (150 on a solid basis)	29	Caramel (73.85)		Available (73)	Ammonia caramel (E150(c))	Available (89)
Caramel IV	Caramel color IV	200 (150 on a solid basis)	29	Caramel (73.85)		Available (73)	Sulfite ammonia caramel (E150(d))	Available (89)
Karaya gum	Karaya gum	Not specified	33	Karaya gum (184.1349)			Karaya gum (E416)	Available (84)
Carnauba wax	Carnauba wax	7	39	Carnauba wax (184.1978)		Available	Carnauba wax (E903)	Available (92)
Carob bean gum	Carob bean gum (Locust bean gum)	Not specified	25	Locust (carob) bean gum (184.1343)		Available	Locust bean gum (E410)	Available (78)
Licorice extract				Licorice and licorice derivatives (184.1408)		Available		
Candelilla wax	Candelilla wax	Acceptable under current use conditions	39	Candelilla wax (184.1976)		Available (81)	Candelilla wax (E902)	Available (92)
Xanthan gum	Xanthan gum	Not specified	30	Xanthan gum (172.695)			Xanthan gum (E415)	Available (92)
Quillaja extract	Quillaja extract	5	29				Quillaja extract (E999)	Available (78)
Gold	Gold	Acceptable under current use conditions	21				Gold (E175)	Available (75)

Name in the list of existing additives	Evaluation by the JECFA (Note 1)			Status in the United States (Note 2)			Status in the EU (Note 3)	
	Name	ADI (mg/kg b.w.)		Name	FDA evaluation	FASEB evaluation	Name	SCF evaluation
Silver							Silver (E174)	Available (75)
Guar gum	Guar gum	Not specified	19	Guar gum (184.1339)		Available	Guar gum (E412)	Available (78)
Guaiac resin	Guaiac resin	2.5	17					
Guaiac resin (extract)	Guaiac resin	2.5	17					
Gutta hang kang				Chewing gum base, Gutta hang kang (172.615)				
Glucanase	β-Glucanase from Aps. niger β-Glucanase from Tricho harzianum	Not specified Not specified	35 39	Carbohydrase and Cellulase derived from Asp. niger (173.120)				
Glucoamylase	Amyloglucosidase from Aps. niger var.	Not specified	35	Amyloglucosidase derived from Rhizopus niveus (173.110)				
Glucose isomerase	Glucose isomerase from Bac. coagulans (immobilized), Glucose isomerase from Str. rubiginous (immobilized), etc.	Not specified Not specified	29 29	Insoluble glucose isomerase enzyme preparations (184.1372)				
Glucose oxidase	Glucose oxidase from Asp. niger	Not specified	18					
L-Glutamine				L-Glutamine (172.320)		Available		
Clove extract				Clove and its derivatives (184.1257)				
Chlorophyll	Chlorophylls	Not limited	13				Chlorophylls and chlorophyllins (E140)	Available (75)
Smoke flavourings	Smoke flavourings	Provisionally acceptable	31	Smoke flavouring solutions		Available (82)		
Higher fatty acid				Fatty acid (172.860)				
Spice extracts				Spices and other natural seasonings and flavorings (182.10): etc.				
Enzymatically decomposed lecithin				Enzyme-modified lecithin (184.1063)	Available (96)			
Cochineal extract				Cochineal extract. carmine (73.100)			Cochineal Carminic acid, Carmines (E120)	Available (79)
Rubber				Chewing gum base, Euphorbiaceae: Natural rubber (172.615)				
Resin of depolymerized natural rubber				Chewing gum base, Euphorbiaceae: Natural rubber (172.615)				
Rice bran wax				Rice bran wax (172.890)				
Psyllium seed gum				Psylium seed husk gum		Available		
Acid clay				Bentonite (184.1155)		Available		

Name in the list of existing additives	Evaluation by the JECFA (Note 1)			Status in the United States (Note 2)			Status in the EU (Note 3)	
	Name	ADI (mg/kg b.w.)		Name	FDA evaluation	FASEB evaluation	Name	SCF evaluation
Cyanocobalamin				Vitamin B_{12} (184.1945)		Available		
Shellac	Shellac	Acceptable under current use conditions	39	Shellac (184.1705, proposed)	Available (89)	Available (82)	Shellac (E904)	Available (92)
Shellac wax				Shellac wax (184.1706, proposed)	Available (89)	Available		
Gellan gum	Gellan gum	Not specified	37	Gellan gum (172.665)	Available (90)		Gellan gum (E418)	Available (92)
Jelutong				Chewing gum base, Apocynacese: Jelutong (172.615)				
Cyclodextrin	β-Cyclodextrin γ-Cyclodextrin	6 (Provisional) Not specified	41 53				β-Cyclodextrin (E459)	
L-Cystine				L-Cystine (72.320)		Available		
Ginger extract				Zinger/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)				
Calcinated calcium				Calcium oxide (184.1210)		Available		
Vegetable carbon black							Vegetable Carbon (E153)	Available (77)
Vegetable lecithin	Lecithin	Not limited	17	Lecithin (184.1400)		Available	Lecithins (E322)	Available (78)
Quicklime	Calcium oxide	Not limited	9	Calcium oxide (184.1210)		Available		
Zein				Zein (184.1984)				
Sage extract				Sage/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)				
L-Serine				L-Serine (172.320)		Available		
Cellulase	Cellulase from Tricho. longibrachiatum	Not specified	39	Carbohydrase and cellulase derived from Asp. niger (173.120)				
Sorva				Chewing gum base, Apocynaceae, Lechecaspi (sorva) (172.615)				
Sorvinha				Chewing gum base, Apocynaceae, Pendare, Perillo (172.615)				
Thaumatin	Thaumatin	Not specified	29				Thaumatin (E957)	Available (89)
Tara gum	Tara gum	Not specified	30				Taragum (E417)	Available (92)
Talc	Talc	Not specified	30				Talc (E553(b))	
Powdered bile	Cholic acid	1.25	17	Ox bile extract (184.1560)		Available		
Tannin (extract)	Tannic acid	Not specified	35	Tannic acid (184.1097)	Available (85)	Available		
Chicle				Chewing gum base, Sapotaceae, Chicle (172.615)				

Name in the list of existing additives	Evaluation by the JECFA (Note 1)			Status in the United States (Note 2)			Status in the EU (Note 3)	
	Name	ADI (mg/kg b.w.)		Name	FDA evaluation	FASEB evaluation	Name	SCF evaluation
Nitrogen	Nitrogen	Acceptable under current use conditions	24	Nitrogen (184.1540)			Nitrogen (E941)	
Tea extract				Tea/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)				
Chilte				Chewing gum base, Euphorbiaceae, Chilte (172.615)				
L-Tyrosine				L-Tyrosine (172.320)		Available		
Tunu				Chewing gum base, Moraceae, Tunu (tuno) (172.615)				
Depolymerized natural rubber				Chewing gum base, Euphorbiaceae: natural rubber (172.615)				
Iron				Iron, elemental (184.1375)		Available		
Dunaliella carotene				β-Carotene (73.95)		Available		
Paprika colour	Paprika oleoresins	Acceptable under current use conditions	35	Paprika oleoresins (73.345)			Paprika extract, capsanthin, capsorbin (E160(c))	
Capsicum water-soluble extract				Capsicum/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)				
d-α-Tocopherol	d-α-Tocopherol, concetrate	0.15-2	30	α-Tocopherols (184-1890)		Available		
Tomato colour							Lycopene (E160(d))	Available (89)
Tragacanth gum	Tragacanth gum	Not specified	29	Gum tragacanth (184.1351)		Available	Tragacanth gum (E413)	Available (84)
Trypsin	Trypsin	Not limited	15	Trypsin (184.1914)		Available		
Trehalose	Trehalose	Not specified	55					
Petroleum naphtha				Petroleum naphtha (172.250)				
Coffee bean extract				Coffee/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)				
Naringin				Naringin/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)		Available (82)		
Niger gutta				Chewing gum base, Moraceae, nigergutta (172.615)				
Nickel				Nickel (184.1537)		Available		
Carrot carotene	Carotene (vegetable)	Acceptable under current use conditions	41	β-Carotene (73.95) Carrot oil (73.300)		Available (80)	Carotenes (E160(a))	
Garlic extract				Garlic and its derivatives (184.1317)		Available		

Name in the list of existing additives	Evaluation by the JECFA (Note 1)			Status in the United States (Note 2)			Status in the EU (Note 3)	
	Name	ADI (mg/kg b.w.)		Name	FDA evaluation	FASEB evaluation	Name	SCF evaluation
Papain	Papain	Not limited	15	Papain (184.1585)		Available		
Palm oil carotene	Carotene (vegetable)	Not limited	41	β-Carotene (73.95)			Carotenes (E160(a))	
Paraffin wax				Paraffin wax (172.886)				
Pancreatin				Pancreatin (184.1583)	Available (95)			
Microcrystalline cellulose	Microcyrstalline cellulose	Not specified	49				Cellulose (E460)	
L-Histidine				L-Histidine (172.320)		Available		
Beet red	Beet red	Not specified	31	Dehydrated beets (73.40)			Beet red (E162)	Available (75)
Pimenta extract				Pimennta/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)				
Furcellaran	Furcellaran	Not specified	28	Furcellaran (172.655)			Furcellaran (E407)	Available (78)
Ficin				Ficin (184.1316)	Available (95)			
Butane				n-Butane and isobutane (184.1165)		Available	Butane (extraction solvent)	
Grape skin colour	Grapeskin extract	25	26	Grape skin extract (enocianina) (73.170)			Anthocyanins (E163)	Available (75)
Protease	Protease from Asp. niger, Protease from Asp. oryzae, var., etc.	Not specified Not specified	35 31	Mixed carbohydrase protease enzyme product (184.1027)				
Propane				Propane (184.1655)		Available	Propane (extraction solvent)	
Bromelain	Bromelain	Not limited	15	Bromelain (184.1024)	Available (95)			
L-Proline				L-Proline (172.320)		Available		
Fractionated lecithin	Lecithin	Not limited	17	Lecithin (184.1400)		Available	Lecithin (E322)	Available (78)
Powdered cellulose	Powdered cellulose	Not specified	20				Cellulose (E460)	Available (78)
Hexane	Hexane	GMP	14	Hexane (173.270)			Hexane (extraction solvent)	
Pectinase	Pectinase from Asp. niger	Not specified	35	Carbohydrase and cellulase derived from Asp. niger (173.120) Carbohydrase derived from Rhizopus oryzae (173.130)				
Pectin	Pectins	Not specified	25	Pectins (184.1588)			Pectin (E440)	Available (78)
Hesperidin				Hesperidine*		Available		
Venezuelan chicle				Chewing gum base, Sapotaceae, Venezuela chicle (172.615)				
Pepper extract				Pepper, black; Pepper, white/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)				
Pepsin	Pepsin (hog stomach)	Not limited	15	Pepsin (184.1595)	Available (95)			

Name in the list of existing additives	Evaluation by the JECFA (Note 1)			Status in the United States (Note 2)			Status in the EU (Note 3)	
	Name	ADI (mg/kg b.w.)		Name	FDA evaluation	FASEB evaluation	Name	SCF evaluation
Heptane	Heptanes	GMP	14					
Hemicellulase	Hemicellulase from Asp.niger, var.	Not specified	35	Carbohydrase and cellulase derived from Asp. niger (173.120) Carbohydrase derived from Rhizopus oryzae (173.130)				
Helium				Helium (184.1355)				
Bentonite				Bentonite (184.1155)		Available		
Microcrystalline wax	Micrcrystalline wax	Not specified	39	Petroleum wax (172.886)			Microcrystalline wax (E905)	
Massaranduba chocolate				Chewing gum base, Sapotaceae, Massaranduba chocolate (172.615)				
Massaranduba balata				Chewing gum base, Sapotaceae, Massaranduba balata (172.615)				
Marigold colour				Tagetes (Aztec marigold) meal and extract (73.295)				
Non-calcinated calcium	Bone phosphate	MTDI 70 mg/kg b.w. (maximum tolerable daily intake for phosphorus from all sources, expressed as P)	29					
Mixed tocopherols	Mixed tocopherol concentrate	2	17	Tocopherols (182.8890)		Available	Tocopherol-rich extract	Available (89)
Bees wax	Bees wax, white and yellow	Acceptable under current use conditions	39	Beeswax (yellow and white) (184.1973)		Available (76)	Bees wax (E901)	Available (92)
Purple sweet potato colour							Anthocyanins (E163)	Available (75)
Purple corn colour							Anthocyanins (E163)	
Purple yam colour							Anthocyanins (E163)	Available (75)
Japan wax				Japan wax*		Available		
Lanolin				Chewing gum base, plasticizing materials, Lanolin (172.615)				
Yolk lecithin	Lecithin	Not specified	17	Lecithins (184.1400)		Available	Lecithins (E322)	Available (78)
L-Lysine				L-Lysine (172.320)		Available		
Lysozyme	Lysozyme hydrochloride	Acceptable under current use conditions	39	Egg white lysozyme (184.1550)		Available (98)	Lysozyme (E1105)	
Lipase	Lipase from Asp. oryzae, var.	Not specified	18	Animal lipase (184.1415) Esterase-lipase derived from Mucor miehei (173.140) Lipase from Rhizopus niveus (184.1420)	Available (98)			

Name in the list of existing additives	Evaluation by the JECFA (Note 1)			Status in the United States (Note 2)			Status in the EU (Note 3)	
	Name	ADI (mg/kg b.w.)		Name	FDA evaluation	FASEB evaluation	Name	SCF evaluation
Liquid paraffin	Mineral oil	20 (High-viscosity) 1 (Medium-viscosity) (provisional) 0.01 (Low-viscousity) (provisional)	51	White mineral oil (172.878)				
Leche de vaca				Chewing gum base, Leche de vaca				
Lemon peel extract				Citrus peel/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)				
Rennet	Rennet bovine, Rennet from Mucor species, etc.	Not limited Not specified	15 18	Rennet (184.1685) Milk-clotting enzymes, microbial (173.150)	Available (93)	Available (77)		
L-Leucine				L-Leucine (172.320)		Available		
Rosidinha				Chewing gum base, Sapotaceae, Roshidinha (rosadinha) (172.615)				
Rosemary extract				Rosemary/Essential oils, oleoresins (solvent-free), and natural extractives including distillates (182.20)				

(Note 1) Numbers in the Remarks column represent the number of the JECFA meeting at which each ADI was established.

(Note 2) CFR Section Numbers for articles are shown in parenthesis in the Name in the United States column.
The FDA or FASEB evaluation columns indicate if safety evaluation results by the FDA or the FASEB were available, with the year of evaluation shown in parenthesis (note that "19" is omitted from the year).
* Not described in the CFR; however, the evaluation results by the FASEB were available.

(Note 3) Food additive numbers in the EU are shown in parenthesis in the Name in the EU column.
The SCF evaluation column indicates if safety evaluation results by the SCF (Scientific Committee for Food) were available, with the year of evaluation shown in parenthesis (year of report publication; note that "19" is omitted from the year).

Table 2. Safety confirmation status of existing additives

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
1	Aureobasidium cultured solution	Thickening stabilizer					
2	Aeromonas gum	Thickening stabilizer					One of the polysaccharides (e.g., xanthan gum) produced by gram-negative bacteria
3	Hollyhock flower extract	Antioxidant					
4	Madder colour	Color				■	
5	Agarase	Enzyme					Enzyme
6	Actinidine	Enzyme					Enzyme
7	Agrobacterium succinoglycan	Thickening stabilizer					
8	Achromopeptidase	Enzyme					Enzyme
9	Acylase	Enzyme				■	
10	Ascorbate oxidase	Enzyme					Enzyme
11	L-Asparagine	Flavoring agent, nutrition fortifier		■			
12	L-Aspartic acid	Flavoring agent, nutrition fortifier		■			
13	Aspergillus terreus extract	Antioxidant					
14	Aspergillus terreus glycoprotein	Food manufacturing agent				■	
15	N-Acetylglucosamine	Sweetener					Monosaccharide
16	α-Acetolactate decarboxylase	Enzyme	■				
17	Azotobacter vinelandii gum	Thickening stabilizer					One of the polysaccharides (e.g., xanthan gum) produced by gram-negative bacteria
18	5'-Adenylic acid	Nutrition fortifier					
19	Annatto extract	Color	■	■	■		
20	Linseed gum	Thickening stabilizer					
21	Aminopeptidase	Enzyme		■			
22	α-Amylase	Enzyme	■	■			
23	β-Amylase	Enzyme	■	■			
24	Almond gum	Thickening stabilizer					
25	L-Alanine	Flavoring agent, nutrition fortifier		■			
26	Gum Arabic	Thickening stabilizer	■	■	■		
27	Arabinogalactan	Thickening stabilizer					Consists of the monosaccharides arabinose and galactose
28	L-Arabinose	Sweetener					Monosaccharide
29	Alkanet colour	Color					
30	L-Arginine	Flavoring agent, nutrition fortifier		■			
31	Alginic acid	Thickening stabilizer	■	■	■		
32	Alginate lyase	Enzyme					Enzyme
33	Aluminium	Color	■		■		

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
34	Aloe vera extract	Thickening stabilizer					
35	Anthocyanase	Enzyme					Enzyme
36	Isoamylase	Enzyme					Enzyme
37	Iso-α-bitter acid	Bitterant, etc.		■			
38	Isomaltodextranase	Enzyme					Enzyme
39	Itaconic acid	Acid				■	
40	Fig leaf extract	Food manufacturing agent					
41	Rice straw ash extract	Food manufacturing agent					Consists of alkali metals and alkaline earth metals
42	Inulinase	Enzyme					Enzyme
43	Polyfructan (inulin type)	Food manufacturing agent					
44	Inositol	Nutrition fortifier		■			
45	Sweet potato carotene	Nutrition fortifier, color	■	■	■		
46	Invertase	Enzyme			■		
47	Welan gum	Thickening stabilizer					One of the polysaccharides (e.g., xanthan gum) produced by gram-negative bacteria
48	Turmeric colour	Color	■	■	■		
49	Udo extract	Preservative					
50	Urushi wax	Gum base, glazing agent					
51	Urease	Enzyme		■			
52	Exomaltotetraohydrolase	Enzyme					Enzyme
53	Japanese styrax benzoin extract	Preservative					Consists mainly of benzoic acid
54	Esterase	Enzyme					Enzyme
55	Shrimp colour	Color					Similar to krill colour
56	Ellagic acid	Antioxidant					
57	Elastase	Enzyme					Enzyme
58	Erwinia mitsuensis gum	Thickening stabilizer					One of the polysaccharides (e.g., xanthan gum) produced by gram-negative bacteria
59	Elemi resin	Thickening stabilizer, gum base					
60	Enju saponin	Emulsifier					
61	Sodium chloride-decreased brine (saline lake)	Flavoring agent					Alkali metals, etc.
62	Enterobacter gum	Thickening stabilizer					One of the polysaccharides (e.g., xanthan gum) produced by gram-negative bacteria
63	Enterobacter simanus gum	Thickening stabilizer					One of the polysaccharides (e.g., xanthan gum) produced by gram-negative bacteria
64	Endomaltohexaohydrolase	Enzyme					Enzyme
65	Endomaltopehtaohydrolase	Enzyme					Enzyme
66	Urucury wax	Gum base, glazing agent					
67	Barley husk extract	Emulsifier, food manufacturing agent					Similar to microcrystalline cellulose and powdered cellulose

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
68	Krill colour	Color				■	
69	Ozokerite	Gum base					
70	Ozone	Food manufacturing agent		■			
71	Opopanax resin	Gum base					
72	Oligo-N-acetylglucosamine	Sweetener					Oligosaccharide
73	Oligogalacturonic acid	Food manufacturing agent					Oligosaccharide
74	Oligoglucosamine	Thickening stabilizer					Oligosaccharide
75	γ-Oryzanol	Antioxidant				■	
76	Oregano extract	Food manufacturing agent		■			
77	Orange colour	Color				■	
78	Seaweed ash extract	Food manufacturing agent					Consists of alkali metals and alkaline earth metals
79	Kauri gum	Gum base					
80	Kaolin	Food manufacturing agent	■	■			
81	Cacao colour	Color				■	
82	Cacao carbon black	Color					Similar to vegetable carbon black
83	Japanese persimmon colour	Color					
84	Granite porphyry	Food manufacturing agent					Mineral
85	Cassia gum	Thickening stabilizer					One of the polysaccharides (e.g., gum arabic) obtained from legume seeds
86	Gastric mucin	Food manufacturing agent					
87	Catalase	Enzyme	■	■			
88	Active carbon	Food manufacturing agent	■				
89	Activated acid clay	Food manufacturing agent					Mineral
90	Gum ghatti	Thickening stabilizer		■			
91	Catechin	Antioxidant					
92	Curdlan	Thickening stabilizer, food manufacturing agent	■	■			
93	Crayfish colour	Color					Similar to krill colour
94	Caffeine (extract)	Bitterant, etc.		■			
95	Carrageenan	Thickening stabilizer	■	■	■		
96	α-Galactosidase	Enzyme		■			
97	β-Galactosidase	Enzyme		■			
98	Mustard extract	Food manufacturing agent		■			
99	Caramel I	Color, food manufacturing agent	■	■	■		
100	Caramel II	Color, food manufacturing agent	■	■	■		
101	Caramel III	Color, food manufacturing agent	■	■	■		
102	Caramel IV	Color, food manufacturing agent	■	■	■		
103	Karaya gum	Thickening stabilizer	■	■	■		

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
104	Carnauba wax	Gum base, glazing agent	■	■	■		
105	Carboxypeptidase	Enzyme					Enzyme
106	Carob germ colour	Color				■	
107	Carob bean gum	Thickening stabilizer	■	■	■		
108	Kawaratake extract	Bitterant, etc.					
109	Rumput roman extract	Preservative					
110	Licorice extract	Sweetener		■			
111	Licorice oil extract	Antioxidant				■	
112	Candelilla wax	Gum base, glazing agent	■	■	■		
113	Xanthan gum	Thickening stabilizer	■	■	■		
114	Xylanase	Enzyme					Enzyme
115	D-Xylose	Sweetener					Monosaccharide
116	Aloe extract	Thickening stabilizer					
117	Chitinase	Enzyme					Enzyme
118	Chitin	Thickening stabilizer				■	
119	Chitosanase	Enzyme					Enzyme
120	Chitosan	Thickening stabilizer, food manufacturing agent					Approved as a Food for Specified Health Uses
121	Redbark cinchona extract	Bitterant, etc.					Consists of the drug quinine, etc.
122	Phellodendron bark extract	Bitterant, etc.					Consists of the drug berberine, etc.
123	Fish scale foil	Color					
124	Quillaia extract	Emulsifier	■		■		
125	Gold	Color, food manufacturing agent	■		■		
126	Silver	Color			■		
127	Guar gum	Thickening stabilizer	■	■	■		
128	Enzymatically hydrolyzed guar gum	Thickening stabilizer				■	
129	Guaiac resin	Antioxidant	■				
130	Guaiac resin (extract)	Gum base	■				
131	Guayule	Gum base					One of those that consist mainly of isoprenes, such as chicle
132	Quercetin	Antioxidant				■	
133	Kusagi colour	Color					
134	Gardenia blue	Color				■	
135	Gardenia red	Color				■	
136	Gardenia yellow	Color				■	
137	Gutta katiau	Gum base					Similar to gutta hang kang
138	Gutta hang kang	Gum base		■			
139	Gutta percha	Gum base					Similar to gutta hang kang

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
140	Cristobalite	Food manufacturing agent					Mineral
141	Green tuff	Food manufacturing agent					Mineral
142	Glucanase	Enzyme	■	■			
143	Curculin	Sweetener					
144	Glucoamylase	Enzyme	■	■			
145	Glucosamine	Thickening stabilizer					Monosaccharide
146	α-Glucosidase	Enzyme					Enzyme
147	β-Glucosidase	Enzyme					Enzyme
148	α-Glucosyltransferase	Enzyme					Enzyme
149	α-Glucosyltransferase treated stevia	Sweetener				■	
150	Glucose isomerase	Enzyme	■	■			
151	Glucose oxidase	Enzyme	■				
152	Glutaminase	Enzyme					Enzyme
153	L-Glutamine	Flavoring agent, nutrition fortifier		■			
154	Grapefruit seed extract	Food manufacturing agent					
155	Kooroo colour	Color					
156	Clove extract	Antioxidant		■			
157	Chlorophylline	Color					Similar to chlorophyll
158	Chlorophyll	Color	■		■		
159	Mulberry bark extract	Food manufacturing agent					
160	Smoke flavourings	Food manufacturing agent	■	■			
161	Diatomaceous earth	Food manufacturing agent					Mineral
162	Spermaceti wax	Gum base, glazing agent					
163	α-Ketoglutaric acid (extract)	Acid					
164	Gentian root extract	Bitterant, etc.					Listed in the JP as Gentian
165	Higher fatty acid	Food manufacturing agent		■			
166	Kojic acid	Food manufacturing agent					
167	Spice extracts	Bitterant, etc.		■			
168	Enzymatically modified isoquercitrin	Antioxidant				■	
169	Enzymatically modified licorice extract	Sweetener					Similar to licorice extract
170	Enzymatically modified soybean saponin	Emulsifier					
171	Enzymatically modified tea extract	Food manufacturing agent					Similar to tea extract
172	Enzymatically modified naringin	Bitterant, etc.					Similar to naringin
173	Enzymatically modified hesperidin	Nutrition fortifier					Similar to hesperidin, which is one of vitamin P
174	Enzymatically modified rutin (extract)	Antioxidant					Similar to rutin (extract)
175	Enzymatically modified lecithin	Emulsifier					Similar to lecithin
176	Enzymatically hydrolyzed licorice extract	Sweetener					Similar to licorice extract
177	Enzymatically hydrolyzed coix extract	Preservative					

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
178	Enzymatically decomposed apple extract	Antioxidant					Enzymatically decomposed apple fruit
179	Enzymatically decomposed lecithin	Emulsifier		■			
180	Yeast cell wall	Thickening stabilizer, food manufacturing agent					Part of yeast
181	Kaoliang colour	Color				■	
182	Cochineal extract	Color		■	■		
183	Bone charcoal	Food manufacturing agent					Similar to vegetable carbon black
184	Bone carbon black	Color					Similar to vegetable carbon black
185	Copaiba balsam	Gum base					
186	Copal resin	Gum base					
187	Cobalt	Food manufacturing agent					Metal
188	Sesame seed oil unsaponified matter	Antioxidant					
189	Sesame straw ash extract	Food manufacturing agent					Consists of alkali metals and alkaline earth metals
190	Rubber	Gum base		■			
191	Resin of depolymerized natural rubber	Gum base		■			
192	Rice bran oil extract	Antioxidant					
193	Enzymatically decomposed rice bran	Antioxidant					
194	Rice bran wax	Gum base, glazing agent		■			
195	Psyllium seed gum	Thickening stabilizer		■			
196	Bamboo grass colour	Color					Similar to chlorophyll
197	Cane wax	Gum base, glazing agent					Similar to bees wax
198	Artemisia sphaerocephala seed gum	Food manufacturing agent, thickening stabilizer					
199	Acid clay	Food manufacturing agent		■			
200	Acid phosphatase	Enzyme					Enzyme
201	Oxygen	Food manufacturing agent					Listed in the JP as a drug
202	Sandarac resin	Gum base					
203	Shea nut colour	Color					
204	Cyanocobalamin	Nutrition fortifier		■			
205	Shellac	Gum base, glazing agent	■	■	■		
206	Shellac wax	Gum base, glazing agent		■			
207	Gellan gum	Thickening stabilizer	■	■	■		
208	Jelutong	Gum base		■			
209	Cyclodextrin	Food manufacturing agent	■		■		
210	Cyclodextrin glucanotransferase	Enzyme				■	
211	Shikon colour	Color					
212	L-Cystine	Flavoring agent, nutrition fortifier		■			
213	Perilla extract	Food manufacturing agent					

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
214	Sandalwood red	Color				■	
215	5'-Cytidylic acid	Nutrition fortifier					
216	Jamaica quassia extract	Bitterant, etc.					
217	Ginger extract	Food manufacturing agent		■			
218	Calcinated calcium	Nutrition fortifier, food manufacturing agent		■			
219	Vegetable sterol	Emulsifier					Similar to cholesterol
220	Vegetable carbon black	Color			■		
221	Vegetable lecithin	Emulsifier	■	■	■		
222	Edible canna extract	Antioxidant					
223	Milt protein	Preservative				■	
224	Hydrogen	Food manufacturing agent					Reducing agent for oils, etc.
225	Sappan colour	Color					
226	Sclero gum	Thickening stabilizer					
227	Stevia extract	Sweetener				■	
228	Powdered stevia	Sweetener					Similar to stevia extract
229	Superoxide dismutase	Enzyme					Enzyme
230	Spirulina colour	Color				■	
231	Sphingolipid	Emulsifier					
232	Quicklime	Food manufacturing agent	■	■			
233	Essential oil-removed fennel extract	Antioxidant					
234	Horseradish extract	Antioxidant, food manufacturing agent					
235	Zein	Food manufacturing agent		■			
236	Zeolite	Food manufacturing agent					Mineral
237	Sesamolin	Antioxidant					
238	Sesamol	Antioxidant					
239	Sage extract	Antioxidant		■			
240	Sesbania gum	Thickening stabilizer					One of the polysaccharides (e.g., gum arabic) obtained from legume seeds
241	Sepiolite	Food manufacturing agent					Mineral
242	Dropwort extract	Antioxidant					
243	L-Serine	Flavoring agent, nutrition fortifier		■			
244	Cellulase	Enzyme	■	■			
245	Crude potassium chloride (sea water)	Flavoring agent					Consists mainly of potassium chloride
246	Crude magnesium chloride (sea water)	Food manufacturing agent					Bittern
247	Buckwheat ash extract	Food manufacturing agent					Consists of alkali metals and alkaline earth metals
248	Sorva	Gum base		■			
249	Sorvinha	Gum base		■			

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
250	L-Sorbose	Sweetener				■	
251	Soybean saponin	Emulsifier					
252	Soybean ash extract	Food manufacturing agent					Consists of alkali metals and alkaline earth metals
253	Thaumatin	Sweetener	■		■		
254	Taurine (extract)	Flavoring agent					Commonly used as a drug (nutrient)
255	Water pepper extract	Food manufacturing agent					
256	Onion colour	Color				■	
257	Tamarind colour	Color				■	
258	Tamarind seed gum	Thickening stabilizer				■	
259	Tara gum	Thickening stabilizer	■		■		
260	Talc	Gum base, food manufacturing agent	■		■		
261	Powdered bile	Emulsifier	■	■			
262	Amino acid-sugar reaction product	Antioxidant					Complex of monosaccharides and amino acids
263	Tannase	Enzyme					Enzyme
264	Tannin	Food manufacturing agent	■	■			
265	Dammar resin	Thickening stabilizer, gum base					
266	Chicle	Gum base		■			
267	Nitrogen	Food manufacturing agent	■	■	■		
268	Tea dry distillate	Food manufacturing agent				■	
269	Tea seed saponin	Emulsifier					
270	Tea extract	Antioxidant, food manufacturing agent		■			
271	Chilte	Gum base		■			
272	L-Tyrosine	Flavoring agent, nutrition fortifier		■			
273	Tunu	Gum base		■			
274	Thujaplicin (extract)	Preservative				■	
275	5'-Deaminase	Enzyme				■	
276	Depolymerized natural rubber	Gum base		■			
277	Theobromine	Bitterant, etc.					Similar to caffeine
278	Dextranase	Enzyme				■	
279	Dextran	Thickening stabilizer					Listed in the JP as a pharmaceutical excipient
280	Iron	Nutrition fortifier, food manufacturing agent		■			
281	Dunaliella carotene	Nutrition fortifier, color		■			
282	Tourmaline	Food manufacturing agent					Mineral
283	Tempeh extract	Antioxidant					
284	Tenryocha extract	Sweetener					
285	Copper	Food manufacturing agent					Metal
286	Paprika colour	Color	■	■	■		

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
287	Capsicum water-soluble extract	Food manufacturing agent		■			
288	Cholesterol	Emulsifier					Listed in the JP as a pharmaceutical excipient
289	Corn colour	Color					
290	Dokudami extract	Antioxidant					
291	Tocotrienol	Antioxidant					
292	d-α-Tocopherol	Antioxidant, nutrition fortifier	■	■			
293	d-γ-Tocopherol	Antioxidant, nutrition fortifier					Similar to d-α-tocopherol
294	d-δ-Tocopherol	Antioxidant, nutrition fortifier					Similar to d-α-tocopherol
295	Tomato colour	Color			■		
296	Tomato glucolipid	Emulsifier					
297	Tragacanth gum	Thickening stabilizer	■	■	■		
298	Transglucosidase	Enzyme					Enzyme
299	Transglutaminase	Enzyme				■	
300	Triacanthos gum	Thickening stabilizer					One of the polysaccharides (e.g., gum arabic) obtained from legume seeds
301	Triacylglycerol lipase	Enzyme					Enzyme
302	Trypsin	Enzyme	■	■			
303	Trehalose	Food manufacturing agent	■				
304	Trehalose phosphorylase	Enzyme					Enzyme
305	Tororoaoi	Thickening stabilizer					
306	Monellin	Sweetener					
307	Rapeseed oil extract	Antioxidant					
308	Bacillus natto gum	Thickening stabilizer, food manufacturing agent					
309	Petroleum naphtha	Food manufacturing agent		■			
310	Coffee bean extract	Antioxidant		■			
311	Soybean extract	Food manufacturing agent					Derived from soy milk
312	Naringinase	Enzyme					Enzyme
313	Naringin	Bitterant, etc.		■			
314	Quassia extract	Bitterant, etc.					
315	Niger gutta	Gum base		■			
316	Absinth extract	Bitterant, etc.					
317	Nystose	Food manufacturing agent				■	
318	Nickel	Food manufacturing agent		■			
319	Nitrilase	Enzyme					Enzyme
320	Olibanum	Gum base					
321	Carrot carotene	Nutrition fortifier, color	■	■	■		
322	Garlic extract	Food manufacturing agent		■			

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
323	Neuraminidase	Enzyme					Enzyme
324	Nordihydroguaiaretic acid	Antioxidant					
325	Roasted rice bran extract	Food manufacturing agent					
326	Roasted soybean extract	Food manufacturing agent					
327	Peroxidase	Enzyme					Enzyme
328	Hachiku extract	Food manufacturing agent					
329	Platinum	Food manufacturing agent					Metal
330	Papain	Enzyme	■	■			
331	Paffia extract	Food manufacturing agent					
332	Palm oil carotene	Nutrition fortifier, color	■	■	■		
333	Perlite	Food manufacturing agent					Mineral
334	Palladium	Food manufacturing agent					Metal
335	Balata	Gum base					One of those that consist mainly of isoprenes, such as chicle
336	Paraffin wax	Gum base, glazing agent		■			
337	Pancreatin	Enzyme		■			
338	Hyaluronic acid	Food manufacturing agent				■	
339	Isodonis extract	Bitterant, etc.					
340	Microcrystalline cellulose	Food manufacturing agent	■		■		
341	Microfibrillated cellulose	Thickening stabilizer, food manufacturing agent					Similar to microcrystalline cellulose and powdered cellulose
342	L-Histidine	Flavoring agent, nutrition fortifier		■			
343	Beet saponin	Emulsifier					
344	Beet red	Color	■	■	■		
345	L-Hydroxyproline	Flavoring agent, nutrition fortifier					Evaluated by the FASEB as a protein component
346	Peanut colour	Color					
347	Sunflower seed extract	Antioxidant				■	
348	Himematsutake extract	Bitterant, etc.					
349	Pimenta extract	Antioxidant		■			
350	Xanthomonas campestris protein	Food manufacturing agent				■	
351	Vermiculite	Food manufacturing agent					Mineral
352	Betel nut extract	Food manufacturing agent					
353	Furcellaran	Thickening stabilizer	■	■	■		
354	Fir balsam	Gum base					
355	Phaffia colour	Color				■	
356	Ficin	Enzyme		■			
357	Phytase	Enzyme					Enzyme
358	Phytic acid	Acid, food manufacturing agent				■	

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
359	Phytin (extract)	Food manufacturing agent					Similar to phytic acid
360	Ferritin	Nutrition fortifier					Similar to heme iron
361	Ferulic acid	Antioxidant					
362	Fukuronori extract	Thickening stabilizer					
363	L-Fucose	Sweetener					Monosaccharide
364	Butane	Food manufacturing agent		■	■		
365	Grape skin colour	Color	■	■	■		
366	Grape skin-derived substance	Food manufacturing agent					
367	Grape seed extract	Antioxidant, food manufacturing agent					
368	Brazilian licorice extract	Sweetener					Similar to licorice extract
369	Fructosyl transferase	Enzyme					Enzyme
370	Fructosyl transferase-treated stevia	Sweetener					Similar to stevia extract
371	Blueberry leaf extract	Antioxidant					
372	Pullulanase	Enzyme				■	
373	Pullulan	Thickening stabilizer, food manufacturing agent				■	
374	Protease	Enzyme	■	■			
375	Propane	Food manufacturing agent		■	■		
376	Propolis extract	Antioxidant					
377	Bromelain	Enzyme	■	■			
378	L-Proline	Flavoring agent, nutrition fortifier		■			
379	Fractionated lecithin	Emulsifier	■	■	■		
380	Powdered cellulose	Food manufacturing agent	■		■		
381	Powdered pulp	Gum base					Similar to microcrystalline cellulose and powdered cellulose
382	Powdered rice hulls	Gum base					Similar to microcrystalline cellulose and powdered cellulose
383	Pecan nut colour	Color				■	
384	Hexane	Food manufacturing agent	■	■	■		
385	Pectinase	Enzyme	■	■			
386	Pectin	Thickening stabilizer	■	■	■		
387	Pectin digests	Preservative					Similar to pectin
388	Hego-ginkgo leaf extract	Antioxidant					
389	Hesperidinase	Enzyme				■	
390	Hesperidin	Nutrition fortifier		■			
391	Hesperetin	Antioxidant					One of vitamin P
392	Betaine	Flavoring agent					
393	Monascus yellow	Color				■	

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
394	Monascus colour	Color				■	
395	Powdered annatto	Color					Similar to annatto extract
396	Carthamus red	Color					
397	Carthamus yellow	Color				■	
398	Venezuelan chicle	Gum base		■			
399	Pepper extract	Antioxidant		■			
400	Pepsin	Enzyme	■	■			
401	Heptane	Food manufacturing agent	■				
402	Peptidase	Enzyme				■	
403	Haematococcus algae colour	Color				■	
404	Hemicellulase	Enzyme	■	■			
405	Heme iron	Nutrition fortifier					Approved as a Food for Specified Health Uses
406	Helium	Food manufacturing agent		■			
407	Benzoin gum	Gum base					
408	Bentonite	Food manufacturing agent		■			
409	Garden balsam extract	Antioxidant					
410	Magnolia obovata extract	Preservative					
411	Hokosshi extract	Food manufacturing agent					
412	Phosphodiesterase	Enzyme					Enzyme
413	Phospholipase	Enzyme					Enzyme
414	Gallic acid	Antioxidant					
415	Jojoba wax	Gum base					
416	Borapet	Bitterant, etc.					
417	Polyphenol oxidase	Enzyme					Enzyme
418	ε-Polylysine	Preservative				■	
419	Microcrystalline wax	Gum base, glazing agent	■	■	■		
420	Macrophomopsis gum	Thickening stabilizer					
421	Mastic gum	Gum base					
422	Madake extract	Food manufacturing agent					
423	Massaranduba chocolate	Gum base		■			
424	Massaranduba balata	Gum base		■			
425	Marigold colour	Color		■			
426	Maltose phosphorylase	Enzyme					Enzyme
427	Maltotriohydrolase	Enzyme					Enzyme
428	Non-calcinated calcium	Nutrition fortifier	■				
429	Citrus seed extract	Food manufacturing agent					
430	Mixed tocopherols	Antioxidant, nutrition fortifier	■	■	■		
431	Bees wax	Gum base, glazing agent	■	■	■		

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
432	Miracle fruit extract	Sweetener					
433	Myrrh	Gum base					
434	Purple sweet potato colour	Color			■		
435	Purple corn colour	Color			■		
436	Purple yam colour	Color			■		
437	Muramidase	Enzyme					Enzyme
438	Methylthioadenosine	Bitterant, etc.					
439	Menaquinone (extract)	Nutrition fortifier				■	
440	Mevalonic acid	Food manufacturing agent					
441	Melaleuca oil	Antioxidant					Essential oil
442	Mousouchiku dry distillate	Food manufacturing agent					Similar to smoke flavourings
443	Mousouchiku charcoal extract	Food manufacturing agent					Similar to vegetable carbon black
444	Mousouchiku extract	Food manufacturing agent				■	
445	Wood chips	Food manufacturing agent					Removed after use as an absorbent
446	Charcoal	Food manufacturing agent					Similar to active carbon
447	Japan wax	Gum base, glazing agent		■			
448	Timber ash	Food manufacturing agent					Consists of alkali metals and alkaline earth metals
449	Timber ash extract	Food manufacturing agent					Consists of alkali metals and alkaline earth metals
450	Rice hull extract	Food manufacturing agent					
451	Peach gum	Thickening stabilizer					
452	Morin	Antioxidant					
453	Montan wax	Gum base, glazing agent					
454	Chinese bayberry extract	Antioxidant				■	
455	Vegetable oil soot colour	Color					Similar to vegetable carbon black
456	Eucalyptus leaf extract	Antioxidant					
457	Yucca foam extract	Emulsifier, food manufacturing agent					
458	Oil stuff seed wax	Gum base, glazing agent					
459	Rakanka extract	Sweetener					
460	Lactoperoxidase	Enzyme					Enzyme
461	Lactoferrin concentrates	Food manufacturing agent					An ingredient of modified dry milk for special purposes
462	Lac colour	Color					
463	Lanolin	Gum base, glazing agent		■			
464	Rhamsan gum	Thickening stabilizer					One of the polysaccharides (e.g., xanthan gum) produced by gram-negative bacteria
465	L-Rhamnose	Sweetener					Monosaccharide
466	Yolk lecithin	Emulsifier	■	■	■		
467	L-Lysine	Flavoring agent, nutrition fortifier		■			

No. of existing additive	Name	Use	JECFA	US	EU	28-Day or longer repeated dose + mutagenicity	Remarks
468	Lysozyme	Enzyme	■	■	■		
469	Lipase	Enzyme	■	■			
470	Lipoxygenase	Enzyme					Enzyme
471	D-Ribose	Sweetener					Monosaccharide
472	Liquid paraffin	Food manufacturing agent	■	■			
473	Linter cellulose	Food manufacturing agent					Similar to microcrystalline cellulose and powdered cellulose
474	Gentian root extract	Antioxidant					
475	Enzymatically decomposed rutin	Antioxidant					
476	Rutin (extract)	Antioxidant				■	
477	Ruthenium	Food manufacturing agent					Metal
478	Mannentake extract	Bitterant, etc.					
479	Leche de vaca	Gum base		■			
480	Levan	Thickening stabilizer		■		■	
481	Lemon peel extract	Food manufacturing agent		■			
482	Forsythia extract	Preservative					
483	Rennet	Enzyme	■	■			
484	L-Leucine	Flavoring agent, nutrition fortifier		■			
485	Logwood colour	Color					
486	Rosidinha	Gum base		■			
487	Rosin	Gum base					
488	Rosemary extract	Antioxidant		■			
489	Wasabi extract	Food manufacturing agent				■	

Table 3. Items for which further collection of information, such as safety study results, etc., is required

No. of existing additive	Name	Use	Distribution status
1	Aureobasidium cultured solution	Thickening stabilizer	×
3	Hollyhock flower extract	Antioxidant	×
7	Agrobacterium succinoglycan	Thickening stabilizer	×
13	Aspergillus terreus extract	Antioxidant	
18	5'-Adenylic acid	Nutrition fortifier	
20	Linseed gum	Thickening stabilizer	
24	Almond gum	Thickening stabilizer	×
29	Alkanet colour	Color	
34	Aloe vera extract	Thickening stabilizer	
40	Fig leaf extract	Food manufacturing agent	×
43	Polyfructan (inulin type)	Food manufacturing agent	×
49	Udo extract	Preservative	×
50	Urushi wax	Gum base, glazing agent	
56	Ellagic acid	Antioxidant	×
59	Elemi resin	Thickening stabilizer, gum base	
60	Enju saponin	Emulsifier	×
66	Urucury wax	Gum base, glazing agent	×
69	Ozokerite	Gum base	
71	Opopanax resin	Gum base	×
79	Kauri gum	Gum base	×
83	Japanese persimmon colour	Color	
86	Gastric mucin	Food manufacturing agent	
91	Catechin	Antioxidant	
108	Kawaratake extract	Bitterant, etc.	×
109	Rumput roman extract	Preservative	
116	Aloe extract	Thickening stabilizer	
123	Fish scale foil	Color	
133	Kusagi colour	Color	
143	Curculin	Sweetener	×
154	Grapefruit seed extract	Food manufacturing agent	
155	Kooroo colour	Color	
159	Mulberry bark extract	Food manufacturing agent	×
162	Spermaceti wax	Gum base, glazing agent	×
163	α-Ketoglutaric acid (extract)	Acid	×
166	Kojic acid	Food manufacturing agent	×
170	Enzymatically modified soybean saponin	Emulsifier	
177	Enzymatically hydrolyzed coix extract	Preservative	
185	Copaiba balsam	Gum base	
186	Copal resin	Gum base	
188	Sesame seed oil unsaponified matter	Antioxidant	
192	Rice bran oil extract	Antioxidant	
193	Enzymatically decomposed rice bran	Antioxidant	×
198	Artemisia sphaerocephala seed gum	Food manufacturing agent, thickening stabilizer	×
202	Sandarac resin	Gum base	
203	Shea nut colour	Color	
211	Shikon colour	Color	
213	Perilla extract	Food manufacturing agent	

No. of existing additive	Name	Use	Distribution status
215	5'-Cytidylic acid	Nutrition fortifier	
216	Jamaica quassia extract	Bitterant, etc.	
222	Edible canna extract	Antioxidant	×
225	Sappan colour	Color	×
226	Sclero gum	Thickening stabilizer	×
231	Sphingolipid	Emulsifier	
233	Essential oil-removed fennel extract	Antioxidant	
234	Horseradish extract	Antioxidant, food manufacturing agent	
237	Sesamolin	Antioxidant	×
238	Sesamol	Antioxidant	×
242	Dropwort extract	Antioxidant	×
251	Soybean saponin	Emulsifier	
255	Water pepper extract	Food manufacturing agent	
265	Dammar resin	Thickening stabilizer, gum base	
269	Tea seed saponin	Emulsifier	
283	Tempeh extract	Antioxidant	×
284	Tenryocha extract	Sweetener	
289	Corn colour	Color	
290	Dokudami extract	Antioxidant	×
291	Tocotrienol	Antioxidant	
296	Tomato glucolipid	Emulsifier	×
305	Tororoaoi	Thickening stabilizer	
306	Monellin	Sweetener	×
307	Rapeseed oil extract	Antioxidant	×
308	Bacillus natto gum	Thickening stabilizer, food manufacturing agent	
314	Quassia extract	Bitterant, etc.	
316	Absinth extract	Bitterant, etc.	
320	Olibanum	Gum base	×
324	Nordihydroguaiaretic acid	Antioxidant	×
325	Roasted rice bran extract	Food manufacturing agent	
326	Roasted soybean extract	Food manufacturing agent	
328	Hachiku extract	Food manufacturing agent	
331	Paffia extract	Food manufacturing agent	
339	Isodonis extract	Bitterant, etc.	×
343	Beet saponin	Emulsifier	×
346	Peanut colour	Color	×
348	Himematsutake extract	Bitterant, etc.	
352	Betel nut extract	Food manufacturing agent	×
354	Fir balsam	Gum base	×
361	Ferulic acid	Antioxidant	
362	Fukuronori extract	Thickening stabilizer	
366	Grape skin-derived substance	Food manufacturing agent	
367	Grape seed extract	Antioxidant, food manufacturing agent	
371	Blueberry leaf extract	Antioxidant	
376	Propolis extract	Antioxidant	
388	Hego-ginkgo leaf extract	Antioxidant	×
392	Betaine	Flavoring agent	
396	Carthamus red	Color	
407	Benzoin gum	Gum base	×

No. of existing additive	Name	Use	Distribution status
409	Garden balsam extract	Antioxidant	×
410	Magnolia obovata extract	Preservative	
411	Hokosshi extract	Food manufacturing agent	
414	Gallic acid	Antioxidant	
415	Jojoba wax	Gum base	
416	Borapet	Bitterant, etc.	×
420	Macrophomopsis gum	Thickening stabilizer	
421	Mastic gum	Gum base	
422	Madake extract	Food manufacturing agent	
429	Citrus seed extract	Food manufacturing agent	×
432	Miracle fruit extract	Sweetener	×
433	Myrrh	Gum base	×
438	Methylthioadenosine	Bitterant, etc.	
440	Mevalonic acid	Food manufacturing agent	×
450	Rice hull extract	Food manufacturing agent	×
451	Peach gum	Thickening stabilizer	×
452	Morin	Antioxidant	
453	Montan wax	Gum base, glazing agent	
456	Eucalyptus leaf extract	Antioxidant	
457	Yucca foam extract	Emulsifier, food manufacturing agent	
458	Oil stuff seed wax	Gum base, glazing agent	×
459	Rakanka extract	Sweetener	
462	Lac colour	Color	
474	Gentian root extract	Antioxidant	×
475	Enzymatically decomposed rutin	Antioxidant	
478	Mannentake extract	Bitterant, etc.	
482	Forsythia extract	Preservative	×
485	Logwood colour	Color	
487	Rosin	Gum base	

× in the distribution status indicates existing food additives that are considered to be no longer distributed in the market in the FY 1999 survey by the Japan Food Additives Association; a total of 51 additives fall under this category.

Annex 1: 14 existing additives

Itaconic acid	Tamarind colour
Orange colour	Xanthomonas campestris protein
Carob germ colour	Phaffia colour
Licorice oil extract	Pecan nut colour
Chitin	Haematococcus algae colour
Enzymatically modified isoquercitrin	Mousouchiku extract
Milt protein	Levan

Annex 1

Itaconic acid

1. Food additive name:

Itaconic acid

2. Origin, method of preparation, and definition:

Itaconic acid is derived from starch or crude sugar by separating the fermentation culture solution of *Aspergillus terreus*. It contains itaconic acid as a component.

3. Major use:

Acid

4. Summary of safety study results:

(1) Single-dose study

The acute oral LD_{50} is considered to be 2.98 g/kg in male mice and 2.65 g/kg in female mice.[1)] Another study has also reported that the acute oral LD_{50} is 5 g/kg in cats, 2 to 4 g/kg in rats, and 6.8 g/kg in mice.[2)]

(2) Repeated-dose study

In a 90-day repeated-dose test in F344 rats by dietary administration (0.25, 0.5, 1.0, and 2.0%), no toxicological effects caused by administration with the substance were observed.[3)] The no observed adverse effect level is considered to be 2.0% (1,748 mg/kg/day in males and 2,158 mg/kg/day in females).

(3) Mutagenicity study

All the results from a reverse mutation test in bacteria,[4)] a DNA repair test in bacteria,[5)] and a chromosomal aberration test in cultured mammalian cells[6)] were judged as negative.

(References)

1. Yamada Akio: Ministry of Health and Welfare FY 1992 Study on Reevaluation, etc. of the Safety of Food Additives, Acute Toxicity Study, Osaka City Institute of Public Health and Environmental Sciences
2. MSDS Canadian Centre for Occupational Health and Safety, AN145503 MSDS-CCOHS, Product Name(s): ITACONIC ACID (STN International search results)
3. Watanabe Hiromitsu, et al.: Ministry of Health and Welfare FY 1997 Study on Reevaluation, etc. of the Safety of Food Additives, Subchronic Toxicity Study of Itaconic

acid, Hiroshima University Research Institute for Radiation Biology Medicine

4. Miyabe Masaki: Ministry of Health and Welfare FY 1992 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (Ames test), Nagoya City Public Health Research Institute
5. Ishizaki Mutsuo: FY 1992 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (Rec-assay), Ibaraki Prefectural Institute of Public Health
6. Toba Masanori: Ministry of Health and Welfare FY 1992 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (Chromosome assay), Yokohama City Institute of Health

Orange colour

1. Food additive name:

Orange colour

2. Origin, method of preparation, and definition:

Orange colour is squeezed from the fruits or pericarps of oranges (*Citrus sinensis* OSBECK) of the Rutaceae family, or obtained by extraction with ethanol, hexane, or acetone at a high temperature followed by removal of the solvent. It consists mainly of fatty acid ester of β-cryptoxanthin as a principal coloring component. Orange colour is yellow.

3. Major use:

Color

4. Summary of safety study results:

(1) Repeated-dose study

In a 13-week repeated-dose test in F344 rats by dietary administration (0.18, 0.55, 1.66, and 5.0%), no toxicological effects caused by administration with the substance were observed.[1)] The no observed adverse effect level is considered to be 5.0% (2.5 g/kg/day), which is the maximum dose.

(2) Mutagenicity study

A reverse mutation test in bacteria was negative regardless of the presence or absence of S9 mix.[2)] In a chromosomal aberration test in cultured mammalian cells, no induction of aberrations was observed in the presence of S9 mix, up to the dose at which cytotoxicity was observed or the limit dose. Structural aberrations were observed in 14% of cells only in the absence of S9 mix in the 2.5 mg/mL short-term treatment group; however, this positive response was not reproduced in an *in vitro* micronucleus test.[3)] In a micronucleus test in mice (2 g/kg, orally administered twice at an interval of 24-hour), no significant increase was observed in the frequency of polychromatophilic erythrocytes with micronuclei.[4)] Orange colour is therefore not considered to have mutagenicity which will cause any particular problem in the body, as the positive response observed in an *in vitro* chromosomal aberration test became negative in the presence of S9 mix and was not reproduced in an *in vitro* micronucleus test, and an *in vivo* micronucleus test performed up to the limit dose was negative.

(References)

1. Furukawa Fumio, et al.: Ministry of Health and Welfare FY 1997 Study on Reevaluation, etc. of the Safety of Food Additives, Subchronic Toxicity Study of Orange colour, National Institute of Health Sciences
2. Miyabe Masaki: Ministry of Health and Welfare FY 1996 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (Ames test), Nagoya City Public Health Research Institute
3. Sofuni Toshio, et al.: Ministry of Health and Welfare FY 1996 Study on Reevaluation,

etc. of the Safety of Food Additives, Chromosomal Aberration Assay in Cultured Mammalian Cells, National Institute of Health Sciences
4. Maita Keizo, et al.: Ministry of Health and Welfare FY 1996 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (mouse micronucleus test), Institute of Environmental Toxicology

Carob germ colour

1. Food additive name:

Carob germ colour

2. Origin, method of preparation, and definition:

Carob germ colour is obtained by grinding the seed germs of carob (*Ceratonia siliqua* LINNE) of the Fabaceae family. Carob germ colour is light yellow.

3. Major use:

Color, food manufacturing agent

4. Summary of safety study results:

(1) Single-dose study

The acute oral LD_{50} is considered to be over 5 g/kg in rats and over 5 g/kg in mice.[1)]

(2) Repeated-dose study

In a 90-day repeated-dose test in F344 rats by dietary administration (0.2, 0.6, 1.7, and 5.0%), no toxicological effects caused by administration with the substance were observed.[2)] The no observed adverse effect level is considered to be 5.0% (2.5 g/kg/day), which is the maximum dose.

(3) Mutagenicity study

All the results from a reverse mutation test in bacteria,[1)] a DNA repair test in bacteria,[1)] and a chromosomal aberration test in cultured mammalian cells[3)] were judged as negative.

(References)

1. Hachiya Noriyuki, et al.: Summary of Results from Acute Toxicity and Mutagenicity Studies with Natural Additives (from FY 1981 to 1983), Toxicology Forum, 8(1), 91-105, 1985
2. Takada Koichi, et al.: 13-Week Subchronic Toxicity Study of Carob Germ Colour in F344 Rats, National Institute of Health Sciences Report, 115, 93-98, 1997
3. Ishidate Motoi, et al.: Mutagenicity Study Results of Food Additives (Part 4), by an FY 1982 Ministry of Health and Welfare Research Grant, Toxicology Forum, 6(6), 671-678, 1983

Licorice oil extract

1. Food additive name:

Licorice oil extract

2. Origin, method of preparation, and definition:

Licorice oil extract is obtained from the residue of the root or rhizome of *Glycyrrhiza uralensis* FISCHER of the Fabaceae family, *Glycyrrhiza inflata* BATALIN of the Fabaceae family, or *Glycyrrhiza glabra* LINNE of the Fabaceae family after washing with water, by extraction at from room temperature to a warm temperature with ethanol, acetone, or hexane. It consists mainly of flavonoids.

3. Major use:

Antioxidant

4. Summary of safety study results:

(1) Single-dose study

The acute oral LD_{50} is considered to be over 5 g/kg in both male and female mice.[1), 2)]

(2) Repeated-dose study

In a 90-day repeated-dose test in F344 rats by dietary administration (0.1, 0.3, 1, and 3%), no toxicological effects caused by administration with the substance were observed.[3)] The no observed adverse effect level is considered to be 3% (1.5 g/kg/day), which is the maximum dose.

(3) Mutagenicity study

All the results from a reverse mutation test in bacteria,[4), 7)] a chromosomal aberration test in cultured mammalian cells,[5)] a DNA repair test in bacteria,[6)] a micronucleus test in mice,[8)] and an umu-test in bacteria[9)] were judged as negative.

(References)

1. Takizawa Yukio: Ministry of Health and Welfare FY 1993 Study on Reevaluation, etc. of the Safety of Food Additives, Acute Toxicity Study, Akita University School of Medicine
2. Acute toxicity of Sankanon (oil-soluble licorice extract), 1985, internal data (unpublished)
3. Nishimura Takahiro: Ministry of Health and Welfare FY 1997 Study on Reevaluation, etc. of the Safety of Food Additives, 90-day treatment study, Hiroshima University
4. Miyabe Masaki: Ministry of Health and Welfare FY 1993 Study on Evaluation of the Safety of Food Additives, Ames test, Nagoya City Public Health Research Institute
5. Sofuni Toshio: Ministry of Health and Welfare FY 1993 Study on Reevaluation, etc. of the Safety of Food Additives, Chromosomal Aberration Test, National Institute of Hygienic Health Sciences

6. Kurita Toshishiro: Ministry of Health and Welfare FY 1993 Study on Reevaluation, etc. of the Safety of Food Additives, Rec-Assay, Institute of Environmental Toxicology
7. Mutagenicity study of Sankanon (oil-soluble licorice extract) in microorganisms, 1985, internal data (unpublished)
8. Micronucleus test of Sankanon (oil-soluble licorice extract), 1985, internal data (unpublished)
9. Short-term mutagenicity study of oil-soluble licorice extract with the umu-test, 1988, internal data (unpublished)

Chitin

1. Food additive name:

Chitin

2. Origin, method of preparation, and definition:

Chitin is obtained from the shells of crustaceans (e.g., shrimps and crabs) or the cuttlebones of squids by removing calcium carbonate at from room temperature to a warm temperature with an acidic aqueous solution, and then removing the protein at a warm to high temperature with a weakly alkaline aqueous solution. Chitin consists of polymers of N-acetyl-D-glucosamine.

3. Major use:

Thickening stabilizer

4. Summary of safety study results:

(1) Repeated-dose study

In a 13-week repeated-dose test in F344 rats by dietary administration (0.2, 0.6, 1.7, and 5.0%), no toxicological effects caused by administration with the substance were observed.[1)] The no observed adverse effect level is considered to be 5.0% (2.5 g/kg/day), which is the maximum dose.

(2) Mutagenicity study

All the results from a reverse mutation test in bacteria,[2)] a chromosomal aberration test in cultured cells,[3)] and a micronucleus test in mice[4)] were judged as negative.

(References)

1. Toyoda Kazuhiro, et al.: Ministry of Health and Welfare FY 1996 Study on Reevaluation, etc. of the Safety of Food Additives, Subchronic Toxicity Study of Chitin, National Institute of Health Sciences
2. Miyabe Masaki: Ministry of Health and Welfare FY 1996 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (Ames test), Nagoya City Public Health Research Institute
3. Sofuni Toshio, et al.: Ministry of Health and Welfare FY 1996 Study on Reevaluation, etc. of the Safety of Food Additives, Chromosomal Aberration Assay in Cultured Mammalian Cells, National Institute of Health Sciences
4. Maita Keizo, et al.: Ministry of Health and Welfare FY 1996 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (mouse micronucleus test), Institute of Environmental Toxicology

Enzymatically modified isoquercitrin

1. Food additive name:

Enzymatically modified isoquercitrin

2. Origin, method of preparation, and definition:

Enzymatically modified isoquercitrin is obtained by adding glucose to a mixture of "Enzymatically decomposed rutin" and starch or dextrin using cyclodextrin glucosyltransferase. It consists mainly of α-glucosyl isoquercitrin.

3. Major use:

Antioxidant

4. Summary of safety study results:

(1) Single-dose study

The acute toxicity LD_{50} is considered to be over 25 g/kg in rats.[1)]

(2) Repeated-dose study

A 90-day repeated-dose and 28-day recovery test were performed in F344/DuCrj rats by dietary administration (0.3, 0.625, 1.25, and 2.5%), and no significant differences were observed in the repeated-dose group in body weight change, while a slight decreasing trend was observed in the male and female 2.5% group of the recovery test group in both the administration period and the recovery period. Urinalysis showed higher ketone body in the male 2.5% group. In addition, autopsy showed yellowing in the femur in both males and females at 1.25% or higher, which was, however, not associated with any histopathological changes. This yellowing was considered to be due to a deposition of the administered substance, and remained after the 28-day recovery period.[2)] Based on these results, the no observed adverse effect level is considered to be 0.625% (394 mg/kg/day in males and 397 mg/kg/day in females).

(3) Mutagenicity study

There were reports of both negative results[3)] and positive results in the high-dose range[4)] in reverse mutation tests in bacteria; however, the reproducibility of these positive results has not been observed. In a chromosomal aberration test in cultured mammalian cells,[5)] a slight increase in abnormal cells was observed only at the highest dose (5 mg/mL) in a 48-hour continuous treatment; however, no dose-response relationship was observed, and this increase is hardly considered to be biologically significant. Taken together with the above results and the negative result of the micronucleus test using mice, it is not considered to have any toxicity for living organisms.

(References)

1. Acute oral toxicity study of Sanmelin 11130 in rats, January 1987, internal data (unpublished)

2. A 90-day repeated-dose and 28-day recovery study of Enzymatically modified isoquercitrin in rats, June 1998, internal data (unpublished)
3. Mutation Study Report in Microorganisms, December 1986, internal data (unpublished)
4. Miyabe Masaki: Ministry of Health and Welfare FY 1998 Study on Evaluation of the Safety of Food Additives, Ames test, Nagoya City Public Health Research Institute
5. Sofuni Toshio: Ministry of Health and Welfare FY 1998 Study on Reevaluation, etc. of the Safety of Food Additives, Chromosomal Aberration Test, National Institute of Hygienic Health Sciences
6. Tani Takayuki: Ministry of Health and Welfare FY 1998 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (mouse micronucleus test), Kanagawa Prefectural Institute of Public Health

Milt protein

1. Food additive name:

Milt protein

2. Origin, method of preparation, and definition:

Milt protein is obtained from nucleic acids and basic proteins in the testicles of *Hexagraos otakii* JORDAN et STARKS of the Hexagrammidae family, *Oncorhynchus gorbuscha* WALBAUM of the Salmonidae family, *Oncorhynchus keta* WALBAUM of the Salmonidae family, *Oncorhynchus nerka* WALBAUM of the Salmonidae family, *Katsuwonus pelanis* LINNAEUS of the Scombridae family, or *Clupea pallasii* VALENCIENNES of the Clupeidae family by decomposition at room temperature in an acidic aqueous solution followed by neutralization. It consists mainly of basic proteins (protamines and histones).

3. Major use:

Preservative

4. Summary of safety study results:

(1) Single-dose study

The acute oral LD_{50} is considered to be over 5 g/kg in mice.[1)]

(2) Repeated-dose study

In a 13-week repeated-dose test in F344 rats by dietary administration (0.625, 1.25, 2.5, and 5.0%), histological test showed a mild atrophy in hepatocytes and the expansion of sinusoids in both males and females at 2.5% or higher.[2)] The no observed adverse effect level is considered to be 1.25% (625 mg/kg/day).

(3) Mutagenicity study

All the results from a DNA repair test in bacteria,[3,4,5)] a reverse mutation test,[6,7,8)] a chromosomal aberration test in cultured mammalian cells,[9)] and an *in vivo* chromosomal aberration test in Chinese hamsters[10)] were judged as negative.

(References)

1. Oral Toxicity Study in Mice, 1986, internal data (unpublished)
2. Tada Yukie, Ikeda Torao, Takahashi Hiroshi, et al.: Subchronic Toxicity Test of Natural Preservative, Milt Protein, in Rats by Dietary Administration, Annual Report of the Tokyo Metropolitan Research Laboratory of Public Health, 49, 267-276, 1998
3. Ishizaki Mutsuo: Ministry of Health and Welfare FY 1989 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity Study (Rec-assay), Ibaraki Prefectural Institute of Public Health
4. Ueno Seiichi and Ishizaki Mutsuo: The DNA Damaging Activity of Natural Food Additives (IV), Food Hygiene and Safety Science, 33(4), 378-382, 1992
5. Deguchi Tetsuo and Mizuno Tomoko: Mutation test and Rec-assay of non-displayed

preservatives, 1986, internal data (unpublished)
6. Sakabe Yoshio: Ministry of Health and Welfare FY 1989 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity Study (Ames test), Nagoya City Public Health Research Institute
7. Fujita Hiroshi, Hirokado Masako, Hirata Keiko, et al.: Annual Report of the Tokyo Metropolitan Research Laboratory of Public Health, 47, 309-313, 1996
8. Mutagenicity study report (reverse mutation test in bacteria), 1987, internal data (unpublished)
9. Sofuni Toshio, et al.: Ministry of Health and Welfare FY 1989 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity Study (Chromosomal Aberration Test), National Institute of Hygienic Health Sciences
10. Yoshida Seiji and Aoki Naoto: Annual Report of the Tokyo Metropolitan Research Laboratory of Public Health, 48, 342-344, 1997

Tamarind colour

1. Food additive name:

Tamarind colour

2. Origin, method of preparation, and definition:

Tamarind colour is obtained from the roasted seeds of Tamarind (*Tamarindus indica* LINNE) of the Fabaceae family by extraction at a warm temperature with a weakly alkaline aqueous solution, followed by neutralization. It consists mainly of flavonoids as principal coloring components. Tamarind colour is red-brown.

3. Major use:

Color

4. Summary of safety study results:

(1) Single-dose study

The acute oral LD_{50} is considered to be over 5 g/kg in mice.[1)]

(2) Repeated-dose study

In a 90-day repeated-dose test in SD rats by dietary administration (1.25, 2.5, and 5.0%), no toxicological effects caused by administration with the substance were observed.[2), 3)] The no observed adverse effect level is considered to be 5.0% (3,278.1 mg/kg/day for males and 3,885.1 mg/kg/day for females), which is the maximum dose.

(3) Mutagenicity study

The results from a reverse mutation test in bacteria[4)] and a chromosomal aberration test in cultured mammalian cells[5)] were judged as negative. In a DNA repair test in bacteria,[6)] a weak response was observed in the high-dose range (3 mg/disk or higher) without S9; however, this weakly positive response disappeared when the metabolic activation system was incorporated. Therefore, it is metabolically inactivated, and is not considered to cause any problems in the body.

(References)

1. Takizawa Yukio: Ministry of Health and Welfare FY 1991 Study on Reevaluation, etc. of the Safety of Food Additives, Study on Acute Toxicity of Natural Additives, Akita University
2. A 90-day (dietary) toxicity study of tamarind colour Coco Brown TRSP(B) in rats, 1997, internal data (unpublished)
3. Mochizuki, M., et al., A 90-day (dietary) toxicity study of tamarind colour Coco Brown TRSP(B) in rats, Japanese Journal of Food Chemistry, 5(2), 140 145, 1998
4. Yamamoto Katsuhiko: Ministry of Health and Welfare FY 1991 Study on the Safety of Food Additives, Mutagenicity (First Study) Ames Test, Nagoya City Public Health Research Institute

5. Sofuni Toshio: Ministry of Health and Welfare FY 1991 Study on Reevaluation, etc. of the Safety of Food Additives, Chromosomal Aberration Assay for Natural Food Additives in Cultured Mammalian Cells, National Institute of Hygienic Health Sciences
6. Ishizaki Mutsuo: Ministry of Health and Welfare FY 1991 Study on Reevaluation, etc. of the Safety of Food Additives, Ibaraki Prefectural Institute of Public Health

Xanthomonas campestris protein

1. Food additive name:

Xanthomonas campestris protein

2. Origin, method of preparation, and definition:

Xanthomonas campestris protein is obtained from *Xanthomonas campestris* INXC-1 cultured in a culture solution consisting of yeast extract, glucose, and magnesium sulfate at room temperature, followed by disruption of the cells at a high pressure. It consists mainly of cytoplasmic proteins.

3. Major use:

Food manufacturing agent

4. Summary of safety study results:

(1) Repeated-dose study

In a 91-day repeated-dose test in Crj:CD(SD) rats by gavage (1 g/kg), no toxicological effects caused by administration with this additive were observed.[1)] The no observed adverse effect level is considered to be 1 g/kg/day.

(2) Mutagenicity study

All the results from a reverse mutation test in bacteria[2)] and a chromosomal aberration test in cultured mammalian cells[3)] were judged as negative.

(References)

1. A 90-day repeated-dose oral toxicity study of *Xanthomonas campestris* protein in rats, 1997, internal data (unpublished)
2. Miyabe Masaki: Ministry of Health and Welfare FY 1997 Study on Reevaluation, etc. of the Safety of Food Additives; Ames test, Nagoya City Public Health Research Institute
3. Nakajima Madoka: Ministry of Health and Welfare FY 1997 Study on Reevaluation, etc. of the Safety of Food Additives; Chromosomal Aberration Test, Biosafety Research Center

Phaffia colour

1. Food additive name:

Phaffia colour

2. Origin, method of preparation, and definition:

Phaffia colour is derived from the culture solution of yeast (*Phaffia rhodozyma* MILLER) by extraction at room temperature with acetone, ethanol, hydrous ethanol, hexane, or a mixture of these, followed by removal of the solvent. It consists mainly of astaxanthin as a principal coloring component. Phaffia colour is clear to red.

3. Major use:

Color

4. Summary of safety study results:

(1) Repeated-dose study

In a 13-week repeated-dose test in F344 rats by dietary administration (0.2, 0.6, 1.7, and 5%, where food concentration is calculated for a Phaffia colour product containing 15% Phaffia colour), no toxicological effects caused by administration with the substance were observed.[1)] The no observed adverse effect level is considered to be 448 mg/kg/day in males and 493 mg/kg/day in females, as Phaffia colour.

(2) Mutagenicity study

All the results from a reverse mutation test in bacteria,[2)] a chromosomal aberration test in cultured mammalian cells,[3)] and a micronucleus test in mice[4)] were judged as negative.

(References)

1. Onodera Hiroshi, et al.: A 13-week Subchronic Toxicity Study of Phaffia Colour in F344 Rats, National Institute of Health Sciences Report, 115, 99-106, 1997
2. Miyabe Masaki: Ministry of Health and Welfare FY 1995 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (Ames test), Nagoya City Public Health Research Institute
3. Toba Masanori: Ministry of Health and Welfare FY 1995 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity Study, First Study, Study on Chromosome Method, Yokohama City Institute of Health
4. Hachiya Noriyuki: Ministry of Health and Welfare FY 1995 Study on Reevaluation, etc. of the Safety of Food Additives, Study on Mutagenicity (micronucleus test), Akita University School of Medicine

Pecan nut colour

1. Food additive name:

Pecan nut colour

2. Origin, method of preparation, and definition:

Pecan nut colour is obtained from the pericarp or astringent skin of pecan nuts (*Carya pecan* ENGL. et GRAEBN.) by extraction at a high temperature with water or hydrous ethanol, or by extraction at a high temperature with an acidic aqueous solution followed by neutralization. It consists mainly of flavonoids as principal coloring components. Pecan nut colour is brown.

3. Major use:

Color

4. Summary of safety study results:

(1) Repeated-dose study

In a 90-day repeated-dose test of Pecan nut colour (containing 60% dextrin) in F344 rats by dietary administration (0.5, 1.5, and 5.0%), no toxicological effects caused by administration with the substance were observed.[1)] The no observed adverse effect level is considered to be 1,287 mg/kg/day (5.0% dose group) in males and 1,344 mg/kg/day (5.0% dose group) in females, as Pecan nut colour. The no observed adverse effect level of this additive containing dextrin is considered to be 3,217 mg/kg/day in males and 3,361 mg/kg/day in females.

(2) Mutagenicity study

In a reverse mutation test in bacteria,[2)] the result was judged as positive in the TA98 strain without S9 in the high-dose range (10 mg/plate or higher); however, it became negative after incorporation of the metabolic activation system. In a chromosomal aberration test in cultured mammalian cells,[3)] no clear induction of structural aberration was observed, although the induction of polyploids was observed. However, the results from a micronucleus test in mice,[4)] which was undertaken for properly high doses, were judged as negative. It is therefore not considered that the induction of polyploids observed *in vitro* will cause any particular problems in the body.

(References)

1. Inoue Tohru: Ministry of Health and Welfare FY 1995 Study on Reevaluation, etc. of the Safety of Food Additives, 90-Day Repeated-Dose Toxicity Study, National Institute of Health Sciences
2. Miyabe Masaki: Ministry of Health and Welfare FY 1995 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (Ames test), Nagoya City Public Health Research Institute
3. Toba Masanori: Ministry of Health and Welfare FY 1995 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (chromosome assay), Yokohama City Institute of Health

4. Hachiya Noriyuki: Ministry of Health and Welfare FY 1995 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (micronucleus test), Akita University School of Medicine

Haematococcus algae colour

1. Food additive name:

Haematococcus algae colour

2. Origin, method of preparation, and definition:

Haematococcus algae colour is the whole algae of *Haematococcus* C.A.AGARCH of the Chlamydomonadaceae family that has been dried and crushed, the extract of this algae with carbon dioxide, or the extract at room temperature with hydrous ethanol, ethanol, acetone, hexane, or a mixture of 2 or more of these, followed by removal of the solvent. It consists mainly of fatty acid esters of astaxanthin as principal coloring components. Haematococcus algae colour is clear to red.

3. Major use:

Color

4. Summary of safety study results:

(1) Repeated-dose study

In a 90-day repeated-dose test in F344 rats by dietary administration (using the drug substance of Haematococcus algae colour, and 0.5, 1.5, and 5.0% as a product (95% soybean oil)), no toxicological effects caused by administration with the substance were observed.[1)] The no observed adverse effect level is considered to be 5.0% (153.2 mg/kg/day for males and 165.2 mg/kg/day for females as drug substance), which is the maximum dose.

(2) Mutagenicity study

All the results from a reverse mutation test in bacteria,[2)] a chromosomal aberration test in cultured cells,[3)] and a micronucleus test in mice[4)] were judged as negative.

(References)

1. Inoue Tohru, et al.: Ministry of Health and Welfare FY 1995 Study on Evaluation, etc. of the Safety of Food Additives, 90-Day Repeated-Dose Toxicity Study of Haematococcus algae colour, National Institute of Health Sciences
2. Miyabe Masaki: Ministry of Health and Welfare FY 1995 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (Ames test), Nagoya City Public Health Research Institute
3. Toba Masanori: Ministry of Health and Welfare FY 1995 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (Chromosome assay), Yokohama City Institute of Health
4. Kishi Michiko: Ministry of Health and Welfare FY 1995 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (micronucleus test), Kanagawa Prefectural Institute of Public Health

Mousouchiku extract

1. Food additive name:

Mousouchiku extract (Mousouchiku extract)

2. Origin, method of preparation, and definition:

Mousouchiku extract is obtained from the crushed skin of the stem of mousouchiku (*Phyllostachys heterocycla* MITF.) of the Poaceae family by extraction at a slightly warm temperature with ethanol. It contains 2,6-dimethoxy-1,4-benzoquinone as a component.

3. Major use:

Food manufacturing agent

4. Summary of safety study results:

(1) Repeated-dose study

In a 4-week repeated-dose test in F344 rats by dietary administration (1 and 5%) and a 90-day repeated-dose test by dietary administration (0.5, 1.0, and 2.0%), no toxicological effects caused by administration with the substance were observed.[1)] The no observed adverse effect level is considered to be 5% (2.5 g/kg/day), which is the maximum dose.

(2) Mutagenicity study

All the results from a reverse mutation test in bacteria[2)] and a chromosomal aberration test in cultured mammalian cells[3)] were judged as negative.

(References)

1. 90-day repeated-dose study of Mousouchiku extract, FY 1996 Survey Report of Chemical Substances, Tumor Prevention Branch of Hiroshima University Research Institute for Radiation Biology Medicine
2. Miyabe Masaki: Ministry of Health and Welfare FY 1996 Study on Reevaluation, etc. of the Safety of Food Additives, Nagoya City Public Health Research Institute
3. Toba Masanori: Ministry of Health and Welfare FY 1996 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study, First Study, Study on Chromosomal Methods, Yokohama City Institute of Health

Levan

1. Food additive name:

Levan

2. Origin, method of preparation, and definition:

Levan is obtained by separation from the fermentation culture solution of sucrose or raffinose by *Bacillus subtilis* (EHR.) COHN. It consists mainly of polysaccharides.

3. Major use:

Thickening stabilizer

4. Summary of safety study results:

(1) Repeated-dose study

In a 178-day repeated-dose test in Wistar rats by dietary administration (prepared as 0.15, 0.5, and 1.5 g/kg/day), no toxicological effects caused by administration with the substance were observed.[1)] The no observed adverse effect level is considered to be 1.5 g/kg/day, which is the maximum dose.

(2) Mutagenicity study

All the results from a reverse mutation test in bacteria[2)] and a chromosomal aberration test in cultured mammalian cells[3)] were judged as negative.

(References)

1. Six-month chronic toxicity study of Levan by dietary treatment in rats, 1994, internal data (unpublished)
2. Miyabe Masaki: Ministry of Health and Welfare FY 1996 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study (Ames test), Nagoya City Public Health Research Institute
3. Takahide Hidenobu: Ministry of Health and Welfare FY 1996 Study on Reevaluation, etc. of the Safety of Food Additives, Mutagenicity study, First Study, Study on Chromosome Method, Yokohama City Institute of Health