GR

ORIGINAL SUBMISSION

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Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, NW
Washington, DC 20004
Tel 202 739 3000
Fax 202 739.3001
www morganlewis com

Morgan Lewis
COUNSELORS AT LAW

RECEIVED
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BY:

Stephen Paul Mahinka
Partner
202 739 5205
smahinka@morganlewis com

May 17, 2007

BY HAND DELIVERY

Office of Food Additive Safety (HFS-255)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Re. Generally Recognized as Safe ("GRAS") Notice for Green Tea Catechin – Kao Corporation

Dear Sir or Madam:

Pursuant to 62 Fed. Reg. 18938 (April 17, 1997), and on behalf of our client Kao Corporation ("Kao"), of Tokyo, Japan, enclosed please find a GRAS Notice for Green Tea Catechin ("GTC"). Kao has determined that GTC is GRAS for use as a natural extract in beverages, including bottled teas, sports drinks, carbonated soft drinks, and juice, based on scientific procedures among experts qualified by scientific training and expertise. This determination is supported by a long history of safe use of green tea and its extracts and the opinion of an outside panel of experts qualified by scientific training and experience to evaluate the safety of GTC as a food ingredient.

On December 15, 2006, Kao met with several FDA officials from the Office of Food Additive Safety, Division of Biotechnology and GRAS Notice Review, to discuss the subject GRAS Notice. Several recommendations and information requests were set forth by FDA at this meeting. These recommendations and requests are listed below, followed by references to where they are addressed in the enclosed GRAS Notice.

1. Identification of polyphenols contained in GTC: The quantity and identity of the polyphenols contained in Kao's GTC are specified in Section III.E, "Typical Product Characteristics."

2. Contaminants from the extraction process: The product specifications, including components other than GTC, are listed in the product specifications in Section III.C, "Specification for Green Tea Catechin."

3. Stability: Stability data are provided in Section III.F, "Stability of GTC."

4. Potential effects of GTC on metabolic enzymes: A discussion of the published literature findings on the effects of GTC on metabolic enzymes is provided in Section VI.D., "Potential Interactions between Green Tea Catechin and Marketed Drugs."

5. Catechin consumption from ingesting green tea: Estimated catechin consumption in the U.S. population from ingesting green tea is provided in Table 4, Section V.C.2, "Catechin Monomer Content Levels."

6. Source of tannase enzyme. The tannase is derived from *Aspergillus oryzea* (see Appendix G).

Please do not hesitate to contact me if there are any questions or further information is required.

Sincerely,

Stephen Paul Mahinka
Counsel for Kao Corporation

Enclosure

GENERALLY RECOGNIZED AS SAFE STATUS OF GREEN TEA CATECHIN

Prepared by

Kao Corporation

May 17, 2007

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I. GENERALLY RECOGNIZED AS SAFE ("GRAS") CLAIM OF EXEMPTION FROM THE REQUIREMENT FOR PREMARKET APPROVAL PURSUANT TO PROPOSED 21 C.F.R. § 170.36(c)(1)

Kao Corporation has determined that Green Tea Catechin is generally recognized as safe ("GRAS") for the intended use, and therefore, exempt from the requirement for premarket approval. As set forth in the following sections, this determination is based on scientific procedures, under the conditions of its intended use in certain beverages, among experts qualified by scientific training and expertise. Therefore, the use of Green Tea Catechin in certain beverages as described below is exempt from the requirement of premarket approval.

Signed, on behalf of Kao Corporation

Ichirou Tokimitsu
Vice President, Global R&D - Health Care
Kao Corporation

A. Name and Address of Notifier

Kao Corporation
2-1-3, Bunka Sumida-ku
TOKYO 131-8501 JAPAN

Contact: Ichirou Tokimitsu
Vice President, Global R&D - Health Care
Telephone: +81-3-5630-7263
Facimile: +81-3-5630-7524
E-mail: tokimitsu.ichirou@kao.co.jp

B. Name of GRAS Substance

The ingredient proposed by Kao Corporation for classification as Generally Recognized as Safe ("GRAS") is **Green Tea Catechin**. Green Tea Catechin (hereafter referred to as "GTC" for purpose of this document only) is a mixture of catechin monomers that is extracted from crude green tea extract.

C. Conditions of Use

GTC is intended for use as a natural extract in beverages, including bottled teas, sports drinks, carbonated soft drinks, and juice. These beverages are identified in the attached appendices according to their respective food codes as listed in the U.S. Department of Agriculture ("USDA") 1994-1996, 98 Continuing Survey of Food Intakes by Individuals ("CSFII 94-96, 98"), and these codes were used to calculate the Estimated Daily Intake ("EDI") values for GTC consumption.[1]

D. Basis for GRAS Determination

Pursuant to 21 C.F.R. § 170.30, Kao Corporation has determined that GTC is GRAS based upon scientific procedures and by the supportive opinion of an outside panel of experts who are qualified by scientific training and experience to evaluate the safety of GTC as a food ingredient ("the Panel").[2] The safety of GTC is supported by a number of published studies on substances that are substantially equivalent to Kao's GTC, including acute, subacute, and chronic studies in rats, *in vitro* mutagenicity studies, and clinical studies of the human tolerance and nutritional effects of GTC. These published studies are supported by Kao's data. Further, the safety and stability of GTC was favorably evaluated by the Ministry of Health and Welfare of Japan and approved for use in foods for specified health use ("FOSHU") in a green tea beverage, an oolong tea beverage, and a

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1 See Appendix A, Appendix B, and Appendix C.

2 See The Generally Recognized as Safe Status of Green Tea Catechin -- Opinion of an Expert Panel (Appendix D). The expert panel consists of: Joseph Borzelleca, Ph.D, James W Anderson, Ph D; Michael W Pariza, Ph D See Appendix E. Qualifications of Expert Panel

sports drink in Japan.[3] The Green tea beverage has been marketed in Japan since May 2003, the oolong tea beverage since March 2005, and the sports drink since May 2006.

E. Uses of Green Tea and Green Tea Extract

Set forth below is a summary of information and reports of prior uses of green tea and green tea extract, as well as the history of use of beverages containing green tea catechins.

1. Prior and Current Use of Green Tea

Asian countries, especially Japan and China, have a long-standing custom of drinking green tea, a dietary habit that began several centuries B.C. in China. Green tea was introduced from China to Japan in the early 8th century and had been used as a medicine. In the 15th century, green tea was used as a beverage among the people of "high society." The custom of drinking tea extended widely in civil society around the late 16th century. At present, the tea plant is cultivated in more than 20 counties of Asia, Africa, and South America as one of the most favorite horticultural plants, analogous to coffee and cocoa.[4]

Green tea is now considered one of the most popular drinks in the world.[5] Of the total amount of tea consumed in the world, approximately 20% is green tea,[6] and both production and consumption are increasing. World green tea production has been forecast to increase from 680,700 tons in 2000 to 900,000 tons in 2010, reflecting an annual average growth rate of 2.6%.[7] Green tea output has expanded faster at 2.5 percent over the past decade compared to 1 percent for black tea.[8]

In the U.S., Americans consumed well over 50 billion servings of tea, or over 2.25 billion gallons in 2005; approximately 12.5% of the tea consumed was green tea.[9] In Canada, there has also been

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3 Ministry of Health, Labor and Welfare, *Permit for Labeling a product as a Food for Specified Health Use* (2003), green tea, Ministry of Health, Labor and Welfare, *Permit for Labeling a product as a Food for Specified Health Use* (2003), oolong tea, Ministry of Health, Labor and Welfare, *Permit for Labeling a product as a Food for Specified Health Use* (2003), sports drink Attached at Appendix F are both the original and English versions The approved specified health use states "[d]ue to a high content of Tea Catechin, this green tea is suitable for people who are concerned about body fat."

4 Yamamoto, T , et al 1997. Chemistry and Applications of Green Tea. CRC Press (New York) p 1

5 Id. at p. 13

6 Mukhtar H. and Ahmad N., 2000 Tea polyphenols prevention of cancer and optimizing health. *Am J Clin Nutr* 71(suppl):1698S-1702S

7 Medium-Term Outlook for Tea, Committee on Commodity Problems, Fourteenth Session of the Intergovernmental Group on Tea, New Delhi, India, 10-11 October, 2001 (http //www fao org/DOCREP/MEETING/003/Y1419E HTM, accessed June 8, 2006) * tonne. metric ton = 1000 kg

8 Current Market Situation and Outlook, Committee on Commodity Problems, Intergovernmental Group on Tea, Fifteenth Session, Colombo, Sri Lanka, 18-20 August 2003. (http //www fao org/es/esc/common/ecg/27747_en_03_2_situation doc; accessed June 8, 2006)

9 http //www teausa com/general/501g cfm - Tea Fact Sheet, accessed June 6, 2006.

an upward trend; total sales of hot and iced tea in Canada were estimated at $267.3 million in 2000 a significant increase since 1999, with green tea reportedly fueling the growth.[10]

In Europe, consumption of green tea has also increased in recent years. Consumption of green tea products in England increased by 87% between 2000 and 2003.[11] In France, green tea accounts for 10.72% of the total sales volume.[12] In Italy, "black teas are still preferred but green teas are becoming more and more successful."[13] In Switzerland, sales of specialty teas have been rising over the past 13 years – the growth is mainly in the green tea sector, "attributed to a desire for a healthy life style and a calming beverage."[14] In Austria, a major tea seller, Demmer Teas, observed that green tea consumption grew from 5% to 26% of total sales from the mid 1990's to the early part of this century.[15]

2. Prior Use of Green Tea Extract

Green tea extract is comprised of polyphenols (catechins, flavonoids, tannins), caffeine, and other minor constituents. Catechin monomers are the primary component of low molecular weight preparations of green tea extract.

Tea extract (which includes green tea extract), which is extracted from green tea leaves, is approved by the U.S. Food and Drug Administration ("FDA") for use in food as a GRAS substance (i.e., natural extractives).[16] Green tea extract is approved for use as a food additive in many countries (e.g., Japan, South Korea) and has been consumed for many years in the context of a variety of applications, including, but not limited to, beverages and dietary supplements.

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10 Market Trends – Green and herbal tea fuel growth of tea sales in Canada, May 15, 2001. Tea Council of Canada. (http //www tea ca/press-trends-green asp?section=media; accessed June 8, 2006).

11 "Positive research driving green tea consumption", nutraingredients com, 01/03/2005 (http //www nutraingredients com/news/ng asp?n=58411-positive-research-driving; accessed June 7, 2006)

12 "Tea Time in Europe," Tea and Coffee, Volume 177, No. 1 Jan./Feb. 2003 (http //www teaandcoffee net/0103/tea htm; accessed June 6, 2006)

13 Id

14 Id

15 Id

16 See 21 C F.R § 182 20, Katsuo, K 1987 Cultural history of Tea *J Food Sci* 117 14-20

F. Availability of Information

The data and information that serve as a basis for this GRAS determination are available for the FDA's review and copying at a reasonable time at the office of:

Morgan, Lewis and Bockius, LLP
1111 Pennsylvania Avenue, N.W.
Washington, DC 20004

Contact: Stephen Paul Mahinka, Esq.
Phone: 202.739.5005
Fax: 202.739.3001
e-mail: smahinka@morganlewis.com

Alternatively, copies of data and information can be provided upon request, by contacting Stephen Paul Mahinka, Esq.

II. IDENTITY

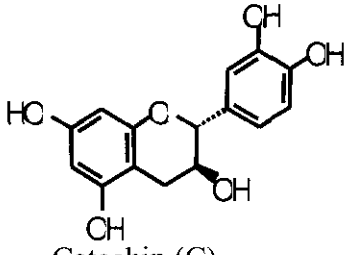
A. Identity

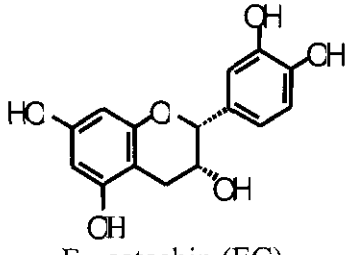
GTC is a natural extract from green tea leaves. It is a brown aqueous solution with a bitter, astringent taste. GTC is a complex mixture of eight catechin monomers, including: catechin ("C"); epicatechin ("EC"); gallocatechin ("GC"); epigallocatechin ("EGC"); catechin gallate ("CG"); epicatechin gallate ("ECG"); gallocatechin gallate ("GCG"); epigallocatechin gallate ("EGCG"). GTC also includes caffeine, organic acids, protein and amino acids, saccharide, and ash.

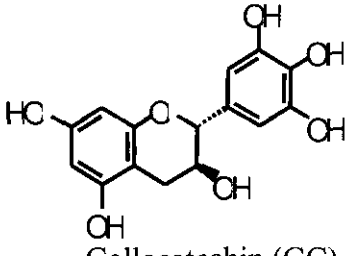
B. Chemical Abstract Service (CAS) Registry Number

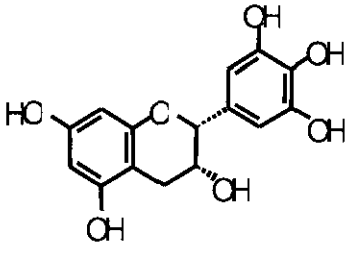
GTC has not been assigned a CAS number.

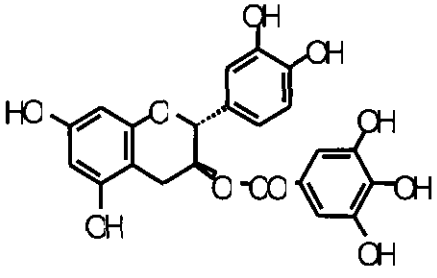
C. Structural Formula

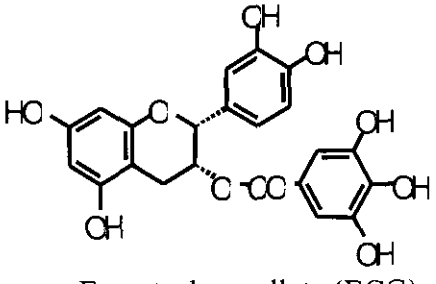

Catechin (C)

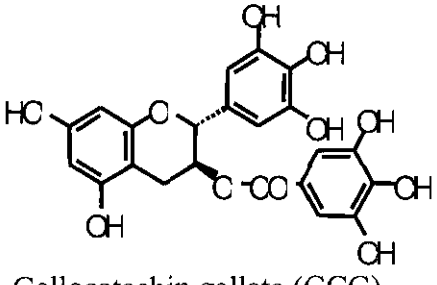

Epicatechin (EC)

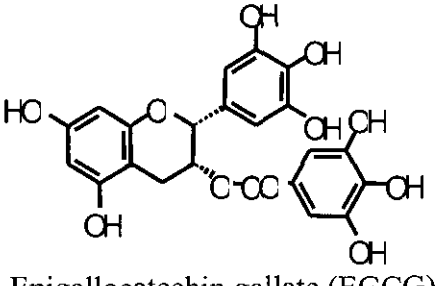

Gallocatechin (GC)


Epigallocatechin (EGC)


Catechin gallate (CG)


Epicatechin gallate (ECG)


Gallocatechin gallate (GCG)


Epigallocatechin gallate (EGCG)

D. Empirical Formula and Molecular Weight

The following are the empirical formulae and molecular weights of the primary components of GTC:

Catechin (C)	($C_{15}H_{14}O_6$)	290.27
Epicatechin (EC)	($C_{15}H_{14}O_6$)	290.27
Gallocatechin (GC)	($C_{15}H_{14}O_7$)	306.27
Epigallocatechin (EGC)	($C_{15}H_{14}O_7$)	306.27
Catechin gallate (CG)	($C_{22}H_{18}O_{10}$)	442.37
Epicatechin gallate (ECG)	($C_{22}H_{18}O_{10}$)	442.37
Gallocatechin gallate (GCG)	($C_{22}H_{18}O_{11}$)	458.37
Epigallocatechin gallate (EGCG)	($C_{22}H_{18}O_{11}$)	458.37

Exemption (b)(4)

Exemption (b)(4)

B. Regulatory Status of Constituents Used in the Manufacturing Process of Green Tea Catechin (GTC)

Constituent	Regulatory Status
Green tea extract (primary ingredient)	21 C.F.R. § 182.20 (GRAS status for tea extract)
Clay	21 C.F.R. § 186.1256 (affirmed as GRAS)
Active carbon	Food Chemicals Codex 5th edition, pp. 94 - 96. CAS No. 7440-44-0 Active carbon is approved for use as a food additive in Japan and is widely used in the manufacturing industry worldwide to refine beverages.
Diatomaceous earth	Food Chemicals Codex 5th edition, pp.137- 138. Natural power and calined powder, CAS No. 61790-53-2 Flux-calined powder, CAS # 68855-54-9 Filtration media (Diatomaceous earth and perlite) is GRAS (GRN000087, 2001). Diatomaceous earth is approved for use as a food additive in Japan and is widely used in the manufacturing industry worldwide to refine beverages.
Powdered cellulose	Food Chemicals Codex 5th edition, pp.109 – 110. CAS No.: 9004-34-6 Powdered cellulose is approved for use as a food additive in Japan. For nearly 85 years, powdered cellulose has served as a food ingredient in United States.
Ethanol	Food Chemicals Codex 5th edition, pp. 157-158. CAS No.: 64-17-5 GRAS for use as a direct food substance (21 C.F.R. § 184.1293

Constituent	Regulatory Status
Tannase (only in "Tannase-treated")	Food Chemicals Codex 5th Edition. Enzyme Commission No.: EC 3.1.1.20 Tannase is approved for use as a food additive in Japan. Tannase is self-GRAS in the United States (Lipton/ Unilever)[19]

[19] This information was provided by the manufacturer of tannase, Kikkoman The published pivotal study supporting the general recognition of safety of tannase is: Lane, RW 1997 Safety evaluation of tannase enzyme preparation derived from *Aspergillus oryzae* Food Chem Toxicol. 35.207-212

C. Specification for Green Tea Catechin (GTC)*

Analyses for three representative batches of GTC are provided in Appendix H.

Main ingredient	**Specification (percentage by weight)**
Total catechin monomers	28 % - 90 %
Polyphenols	37 % - 100%
Other Components	
Caffeine	Not more than 7 %
Organic acids	Not more than 10 %
Protein and Amino Acids	Not more than 10 %
Saccharide	Not more than 12 %
Fiber	Not more than 1 %
Fat	Not more than 1 %
Ash	Not more than 5%
Microbiological	
Total plate count	undetectable
Colon *bacillus*	undetectable
Heavy metal	
Arsenic	below detection limit (<0.2 ppm)
Sn	not more than 150 ppm
Cadmium	below detection limit (<0.1 ppm)
Lead	below detection limit (<0.4 ppm)

*Microbiological and heavy metal specifications are applied to the beverage form.

D. Analytical Methods

The analytical methods used for these measurements are listed below.

Analyte	Method
Total Catechin monomers	HPLC-Method (Kao method)
Polyphenols	Tartaric Acid-Method (Kao method)[20]
Caffeine	HPLC-Method (analyzed by Japan Food Research Laboratories)
Organic acids	HPLC-Method (analyzed by Japan Food Research Laboratories)
Protein and Amino Acids	Kjeldahl-Method (analyzed by Japan Food Research Laboratories)
Saccharide	HPLC-Method (analyzed by Japan Food Research Laboratories)
Fiber	Enzymatic-gravimetric Method (analyzed by Japan Food Research Laboratories)
Fat	Acid hydrolysis (analyzed by Japan Food Research Laboratories)
Ash	Ignition at 550° (analyzed by Japan Food Research Laboratories)
Total plate count	JFSL method[21]
Colon bacillus	JFSL method[22]
Arsenic	JFSL method[23]
Sn	JFSL method[24]

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20 ***Reagents***: Ferrous tartrate solution: Dissolve 100mg of $FeSO_4$-$7H_2O$ and 500mg of Rochelle salt in water and dilute to 100ml, Sorensen's phosphate buffer solution: Mix M/15 disodium hydrogenphosphate solution (11 867g Na_2HPO_4 $2H_2O$/L) with M/15 potassium dihydrogenphosphate solution (9.073g KH_2PO_4/L) and adjust pH at 7 5; Ethyl gallate standard solution: Pure and dried (100°C, 1hr) ethyl gallate containing 5-25mg per 100mL in 5 mg increments.

Preparation of Calibration Curve: Pipet into 25mL volumetric flasks 5mL aliquots of the ethyl gallate standard solutions Add 5mL of ferrous tartrate solution and dilute to the mark with phosphate buffer solution Determine absorbance of each colored solution against blank at 540nm. Absorbance of 1mg of ethyl gallate is equal to that of 1.5mg of tea tannin (catechin)

Measurement: Dissolve 0.5g of instant green tea (IGT) in water and dilute to 100mL Pipet 5mL of IGT solution and 5mL of ferrous tartrate solution into 25mL volumetric flask and dilute to the mark with phosphate buffer solution Develop the color and determine the absorbance Read the ethyl gallate content from the calibration curve and calculate the tannin content multiplying the ethyl gallate content by 1 5

21 These measurements were derived based on the methods set forth under Japanese Law Food Sanitation Law (2002) (Japan), pp 879-81

22 These measurements were derived based on the methods set forth under Japanese Law Food Sanitation Law (2002) (Japan), pp 881-882

23 This atomic absorption spectrometry method was derived based on the methods set forth under Japanese Law Food Sanitation Law (2002) (Japan), pp 844-45

24 Id.

Analyte	Method
Cadmium	JFSL method[25]
Lead	JFSL method[26]

E. Typical Product Characteristics

Catechins and Polyphenol	Green Tea Catechin Ingredient (W/W%)	Tannase-treated Green Tea Catechin Ingredient (W/W%)
Total Catechin Monomers		
Polyphenols		
Polyphenols (except catechins)[27]		
Catechin Profile		
Gallocatechin (GC)		
Epigallocatechin (EGC)		
Catechin (C)		
Epicatechin (EC)		
Epicatechin gallate (ECG)		
Epigallocatechin gallate (EGCG)		
Gallocatechin gallate (GCG)		
Catechin gallate (CG)		

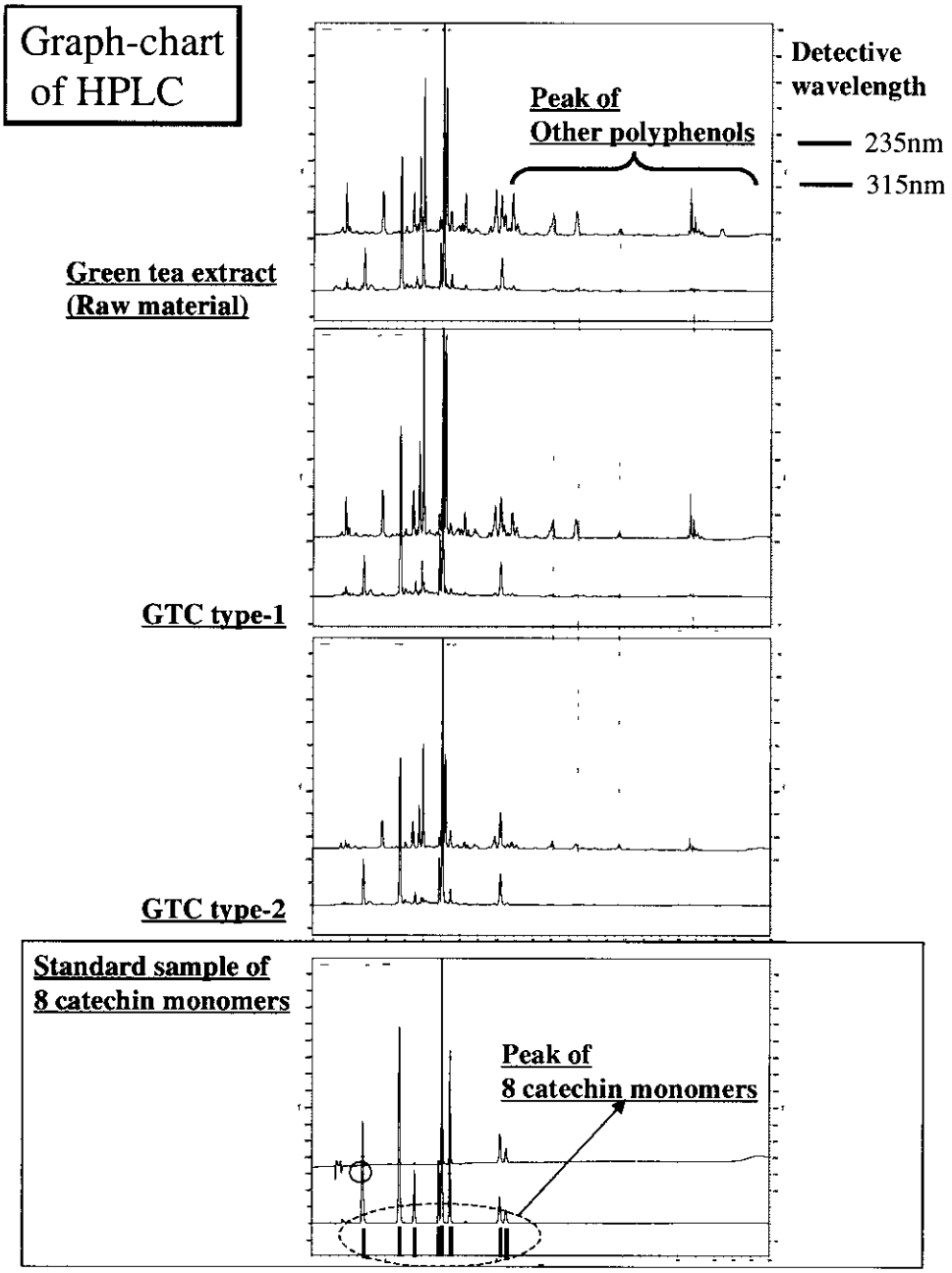
25 Id

26 This Na2C calorimetric method was derived based on the methods set forth under Japanese Law Food Sanitation Law (2002) (Japan), pp 849-50

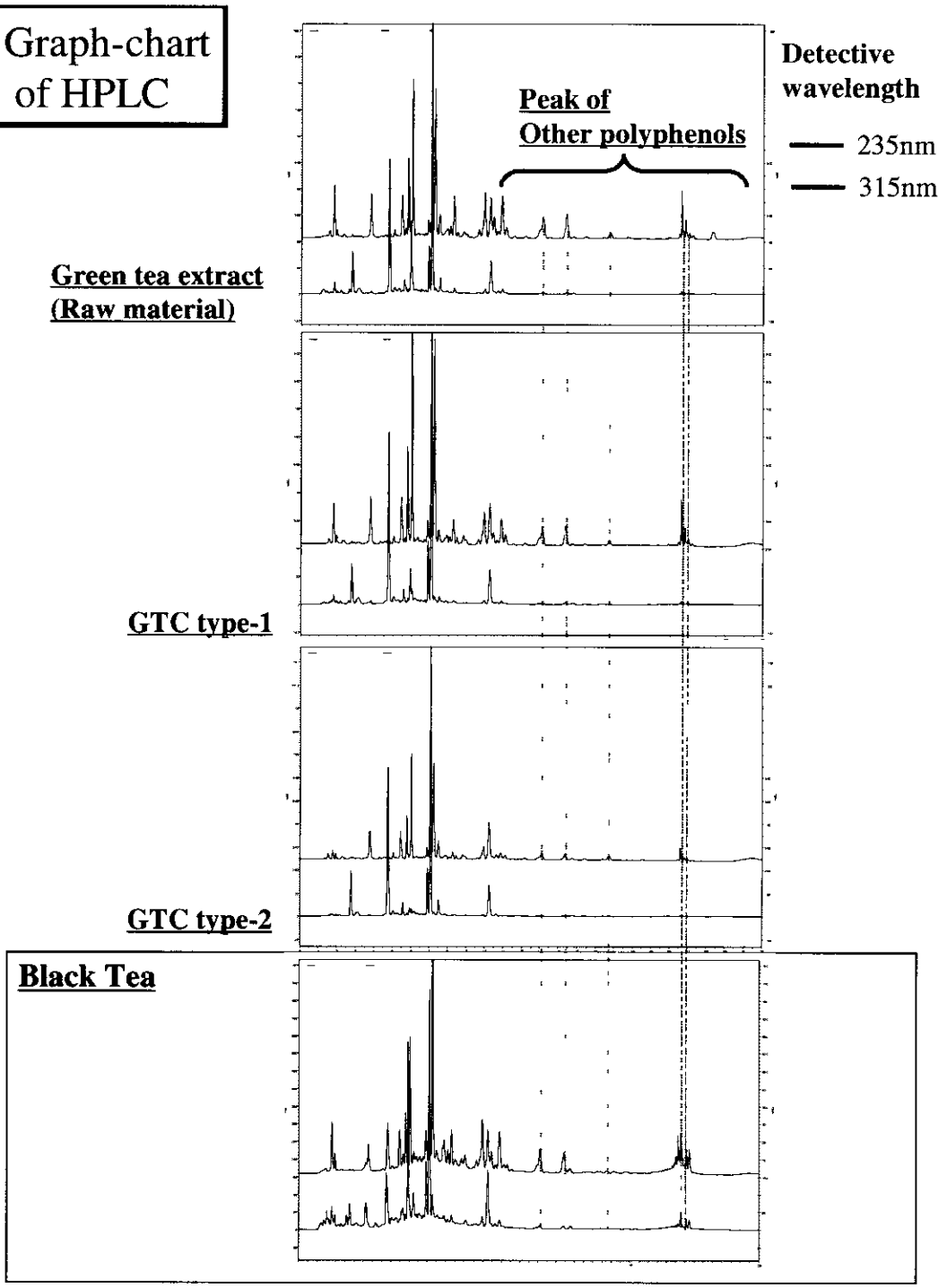
27 The additional polyphenols in GTC are primarily polymeric flavan-3-ols (proanthocyanidins) Many different varieties of proanthocyanidins are found in green tea and green tea extract, including: procyanidin B-2, procyanidin B-2 3,3'-di-O-gallate, prodelphinidin B-2 3,3'-di-O-gallate, procyanidin B-3; procyanidin B-4, prodelphinidin B-4 3'-di-O-gallate, and procyanidin C-1 (Ina K , et al. 2003 Chemical composition and function of TEA. Kogaku Publishing Co , (Tokyo) p 11) Individual proanthocyanidins are present in GTC at levels too low for quantification

HPLC Graph of GTC:

The following HPLC graphs show the chemical profile of green tea extract (raw material), Heat-treated GTC (or ("GTC type 1), a non-heat treated version of GTC ("UT-GTC" or "GTC Type 2") and a standard sample of 8 catechin monomers. As shown in the graphs below, the peak pattern of other polyphenols are the same for all of these preparations. Accordingly, other polyphenols in GTC are passed from green tea extract (raw material) to GTC and UT-GTC. Peak values of GTC and UT-GTC are lower compared to green tea extract. The content level of other polyphenols is decreased by the purification process.



The following graphs are HPLC-graphs of green tea extract, GTC, UT-GTC and Black tea. Peak patterns of other polyphenols are nearly identical, thus, it is clear that the other polyphenols present in GTC are derived from tea leaves.



F. Stability of GTC

The stability of GTC was assessed with GTC that was stored in three layers of laminated packaging at -20° C and normal atmospheric pressure (Kao's standard storage condition) for greater then one year. The substance was then evaluated and compared to the specifications of GTC analyzed immediately after the manufacturing process. Total catechin monomers and polyphenols remained almost unchanged under the standard storage conditions.

Stability Data for GTC (GTC, Lot No. 0310242; Run 1)

	0 months	14 months	18 months	Specification
Total catechin monomers	44.2 %	44.1%	42.9%	28 % - 90 %
Polyphenols	51.3 %	51.8 %	51.9 %	37 % - 100%

Stability data for GTC (GTC, Lot No.0310242; Run 2)

	0 months	14 months	18 months	Specification
Total catechin monomers	42.8 %	43.8%	42.6%	28 % - 90 %
Polyphenols	53.5 %	52.8 %	54.2 %	37 % - 100%

Stability data for Heat-treated GTC (Heat-treated GTC, Lot No.0502271)

	0 months	12 months	18 months	Specification
Total catechin monomers	62.0 %	62.0 %	63.2%	28 % - 90 %
Polyphenols	66.0 %	66.0 %	65.6 %	37 % - 100%

Stability of GTC (total catechin monomers) in Beverages:

As discussed above, GTC is intended for use as a natural extract in beverages, including bottled teas, sports drinks, carbonated soft drinks, and juice. Each beverage contains approximately 540 mg of total catechin monomers (i.e., the main ingredient of GTC). The following stability data for total catechin monomers were collected following storage at 25° C and 37° C in prepared beverage form. These data demonstrate that in a closed bottle (or can) filled with beverage containing GTC total catechin monomers are stable for at least 6 months at temperatures up to 37° C.

Stability data of GTC (total catechin monomers) in Oolong tea beverage

Storage condition A -- Temperature: 25° C, 6-month storage

	0 months	1 month	3 months	5 months	6 months
Total catechin monomers (PET Bottle /350ml)	599mg (100%)	595mg (99%)	588mg (98%)	581mg (97%)	581mg (97%)
Total catechin monomers (Steel Can /340ml)	581mg (100%)	575mg (99%)	569mg (98%)	571mg (98%)	571mg (98%)

Storage condition B -- Temperature: 37°, 2-month storage

	0 month	1 month	2 month
Total catechin monomers (PET Bottle /350ml)	599mg (100%)	581mg (97%)	574mg (96%)
Total catechin monomers (Steel Can /340ml)	581mg (100%)	561mg (97%)	558mg (96%)

Stability data of GTC (total catechin monomers) in sports drink
GTC: GTC type-2
Storage condition A -- Temperature: 25°, 6-month storage

	0 months	1 month	3 months	5 months	6 months
Total catechin monomers (PET Bottle /500ml)	625mg (100%)	606mg (97%)	594mg (95%)	581mg (93%)	569mg (91%)
Total catechin monomers (Steel Can /480ml)	600mg (100%)	600mg (100%)	582mg (97%)	570mg (95%)	570mg (95%)

Storage condition B -- Temperature: 37°, 2-month storage

	0 months	1 month	2 months
Total catechin monomers (PET Bottle /500ml)	625mg (100%)	600mg (96%)	575mg (92%)
Total catechin monomers (Steel Can /340ml)	600mg (100%)	582mg (97%)	558mg (93%)

IV. SELF-LIMITING LEVELS OF USE

Although no limits on the use of GTC have been established, its bitter, astringent taste likely would limit its use at high levels.

V. ESTIMATED CONSUMPTION OF TEA CATECHIN

A. Daily Consumption of Green Tea in Japan

Drinking green tea is an integral part of Japanese life-style, where it is consumed in many aspects of daily life. Typically, Japanese people drink 1-2 cups of green tea daily. Local residents of some areas (e.g., Shizuoka, Saitama, and Miyagi) drink as many as 10 cups of green tea daily (1000–1500 mg of tea catechin/person/day).[28]

Daily consumption of green tea in the U.S. is discussed in Section V.C.1 below.

B. Catechin Monomer Content of Green Tea and Other Tea Beverages

Catechin monomers are the largest component of the low molecular weight fraction of green tea. The relative composition of catechin monomer content differs between green tea and fermented tea (i.e., black tea and oolong tea), and also due to a variety of manufacturing process conditions (e.g., extraction, filtration, and fermentation).[29] The catechin monomer levels of green tea and other tea beverages are provided in Table 2.

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28 Muramatsu, K 1991 *Science of Tea.* Asakura Publishing Co (Tokyo), p. 153; Imai, K. 1997. Cancer Prevention Effects of Drinking Green Tea among a Japanese Population, *Preventive Medicine.* 26. 769-775; Suga, K. 1998. Phase I clinical trial with green tea tablets in a Japanese healthy population *Cancer Prevention International* 3· 79-88 , Sato, Y 1989. Possible contribution of green tea drinking habits to the preventuion of stroke *Tohoku J. Exp Med.* 157.337-343

29 Saitou, N. 1998 Study on tea drinks. contents of catechins, caffeine, and total amino acid *Report of Consumer Science Research Institute of Hyogo Prefecture* 13·242. [Japanese]; Muramatsu, K 1991 *Science of Tea* Asakura Publishing Co (Tokyo), p. 153.

Table 2. Catechin Monomer Levels of Green Tea and Other Tea Beverages

		Total Catechin Monomer Content (mg/100 mL)
Saitou, 1998*	Brewed green tea (10 leaf samples)	111.17
	Green tea beverage products (21 products)	6.89
	Brewed oolong tea (10 leaf samples)	15.52
	Oolong tea beverage products (15 products)	10.57

* Based on data from this study, 10 cups of green tea contains **1665 mg of Catechin monomers**.

C. Daily Consumption of Green Tea Catechin (GTC) in the United States

1. Green Tea Consumption

Green tea consumption estimates for the U.S. population were derived from USDA's 1994-96 and 1998 Continuing Survey of Food Intakes by Individuals ("CSF II 94-96, 98"), which is a nationally representative survey that collected 2-day food intake data, in addition to demographic information, for approximately 22,000 individuals. Only individuals with complete and reliable 2-day dietary records were included in the analyses (N=20,607). The 2-day average estimated green tea consumption in the U.S. is provided in Table 3.

Table 3. 2-Day Average Estimated Green Tea Consumption in the U.S.

Population	% Consumers	Unweighted number of consumers[30]	Weighted per-user 2-day consumption (g/day)	
			Mean	90th Percentile
US population (2+ years)	12 73%	1733	363 3	715 9
Children 2-6	2 25%	141	129.6	237.3†
Children 7-12	3 63%	51	177.9	240†
Males 13-19	3.25%	22	430.2	711 7†
Females 13-19	7.03%	45	246 7	470 7†
Males 20+	12.79%	622	418 1	826
Females 20+	19.15%	852	348	716 2

† Indicates estimates are not statistically valid. The unweighted number of consumers does not meet the minimum sample size required to estimate intake at the 90th percentile

2. Catechin Monomer Content Levels

The levels of catechin monomer used in this analysis were obtained from the USDA Database for the Flavanoid Content of Selected Foods (USDA, 2003).[31] Catechin monomer intakes were derived by combining the mean catechin concentration in green tea beverages with the tea consumption levels reported in Table 3. Resulting estimates are summarized in Table 4. The mean and 90th percentile of the distribution of catechin monomer intakes associated with green tea consumption were **200 mg/day** and **393 mg/day**, respectively, for consumers of green tea among the Total U.S. population.

30 The estimates in the tables in this section rely on consumption data extracted from USDA's 1994-96 & 1998 CSFII The CSFII surveys oversample children, low income individuals, and certain ethnic and racial subpopulations Thus, the data generated by these surveys cannot be used as is, without adjusting for the differential probability of selection USDA includes in its database "sampling" weights that should be used in order for the summary estimates (e.g., means and percentiles) derived from the data to be representative of the U S population. The summary estimates that are provided in the tables in this section are derived using these weights. However, one needs to examine the actual number of subjects in the subpopulation of interest, or the "UNWEIGHTED NUMBER," because if that number is small, then the estimate derived from the consumption data for this subpopulation would be unreliable. (See page 42 of the document at: http //www ars.usda gov/SP2UserFiles/Place/12355000/pdf/scs_all.PDF for more details and examples)

31 This publicly available database can be accessed at http //www nal usda gov/fnic/foodcomp/Data/Flav/flav html.

Table 4. 2-Day Average Estimated Catechin Intake Associated with the Consumption of Green Tea

Population	Catechin	% Consumers	Unweighted number of consumers	Per-user 2-day consumption (mg/day)	
				Mean	90th Percentile
US population (2+ years)	Total Catechins	12 73%	1733	200	393
	(+)-Catechin			10	20
	(-)-Epigallocatechin			34	67
	(-)-Epicatechin			16	32
	(-)-Epicatechin 3-gallate			44	86
	(-)-Epigallocatechin 3-gallate			96	189
	(+)-Gallocatechin			0	0
Children 2-6	Total Catechins	2 25%	141	71	130
	(+)-Catechin			4	7
	(-)-Epigallocatechin			12	22
	(-)-Epicatechin			6	11
	(-)-Epicatechin 3-gallate			16	28
	(-)-Epigallocatechin 3-gallate			34	63
	(+)-Gallocatechin			0	0
Children 7-12	Total Catechins	3 63%	51	98	132
	(+)-Catechin			5	7
	(-)-Epigallocatechin			17	22
	(-)-Epicatechin			8	11
	(-)-Epicatechin 3-gallate			21	29
	(-)-Epigallocatechin 3-gallate			47	63
	(+)-Gallocatechin			0	0
Males 13-19	Total Catechins	3 25%	22	236	391
	(+)-Catechin			12	20
	(-)-Epigallocatechin			40	66
	(-)-Epicatechin			19	32
	(-)-Epicatechin 3-gallate			52	85
	(-)-Epigallocatechin 3-gallate			113	188
	(+)-Gallocatechin			0	0
Females 13-19	Total Catechins	7.03%	45	136	259
	(+)-Catechin			7	13
	(-)-Epigallocatechin			23	44
	(-)-Epicatechin			11	21
	(-)-Epicatechin 3-gallate			30	56
	(-)-Epigallocatechin 3-gallate			65	124
	(+)-Gallocatechin			0	0
Males 20+	Total Catechins	12 79%	622	230	454
	(+)-Catechin			12	23
	(-)-Epigallocatechin			39	77
	(-)-Epicatechin			19	37
	(-)-Epicatechin 3-gallate			50	99
	(-)-Epigallocatechin 3-gallate			110	218
	(+)-Gallocatechin			0	0

Population	Catechin	% Consumers	Unweighted number of consumers	Per-user 2-day consumption (mg/day)	
				Mean	90th Percentile
Females 20+	Total Catechins	19 15%	852	191	393
	(+)-Catechin			10	20
	(-)-Epigallocatechin			32	67
	(-)-Epicatechin			16	32
	(-)-Epicatechin 3-gallate			42	86
	(-)-Epigallocatechin 3-gallate			92	189
	(+)-Gallocatechin			0	0

D. Estimated Daily Intake of Green Tea Catechin (GTC) in the United States

The consumption of GTC from all proposed uses was estimated using USDA CSFII 1994-1996 and the USDA CSFII 1998. The following scenarios were used to assess the daily intake of GTC:

Scenario 1: Consumers of all bottled tea in the U.S. will switch to proposed beverage

Scenario 2: Consumers of sports drinks in the U.S. will switch to proposed beverage

Scenario 3. Consumers of carbonated beverages and juices in the U.S. will switch to proposed beverage

Scenario 4: Consumers of combined bottled tea, sports drinks, carbonated beverages, and juices in the U.S. will switch to proposed beverage

The potential intake of GTC from each of these scenarios is present in Table 5.

Table 5. Summary of the Assessment of Potential Intake of GTC

Scenario	Potential Intake of GTC		
	Mean (90th Percentile) mg/day	Mean (90th Percentile) mg/kg-bw/day	Unweighted Number of Users (% Users)
#1. Bottled Tea			
US Population (2+ years)	**297 (545)**	**4.3 (7.8)**	**991 (7.39)**
Children (2 to 6 years)	148 (246)	7 9 (12.0)	106† (1.919)
Children (7 to 12 years)	187 (256)	5.4 (7.4)	40† (3 39)
Males (13 to 19 years)	323 (550)	4 7 (8.3)	55† (8.87)
Females (13 to 19 years)	251(492)	4.4 (7 2)	47† (8.07)
Males (20+ years)	334 (560)	4.1 (7.8)	414 (9 58)
Females (20+ years)	275 (495)	4 2 (7.7	329 (7.19)
#2. Sports Drinks			
US Population (2+ years)	**372 (761)**	**6.5 (13.6)**	**422 (2.2)**
Children (2 to 6 years)	190 (321)	10.8 (18.8)	178† (2.95)
Children (7 to 12 years)	252 (514)	7 5 (14.5)	51† (3 64)
Males (13 to 19 years)	484 (1016)	6.9 (15.7)	43† (7 50)
Females (13 to 19 years)	319 (873)	5.9 (15 9)	14† (1.83)
Males (20+ years)	451 (1014)	5.6 (11.8)	106† (2.55)
Females (20+ years)	268 (510)	4.4 (7 9)	30† (0.69)
#3. Carbonated beverage and Juice			
US Population (2+ years)	**584 (1172)**	**10.2 (21.2)**	**15292 (84.06)**
Children (2 to 6 years)	375 (697)	21 2 (39.7)	5454 (90 27)
Children (7 to 12 years)	489 (898)	14 0 (25.3)	1358 (88 64)
Males (13 to 19 years)	953 (1775)	14.3 (26.2)	575 (94.80)
Females (13 to 19 years)	648 (1269)	11.5 (22.2)	584 (94.02)
Males (20+ years)	674 (1331)	8.2 (16.3)	3766 (83.3)
Females (20+ years)	504 (1012)	7 6 (15 5)	3555 (79 53)
#4. Combined Bottled Tea, Sports Drinks, Carbonated Beverages and Juices			
US Population (2+ years)	**602 (1217)**	**10.4 (21.5)**	**16635 (84.29)**
Children (2 to 6 years)	378 (701)	21 3 (39.9)	4955 (90.92)
Children (7 to 12 years)	495 (918)	14.2(25.6)	1490 (87.74)
Males (13 to 19 years)	977 (1792)	14.7 (27 0)	
Females (13 to 19 years)	666 (1278)	11.8 (22.3)	
Males (20+ years)	701 (1372)	8.5 (17 1)	
Females (20+ years)	517 (1036)	7.8 (16 0)	

† Indicates estimates are not statistically valid. The unweighted number of consumers does not meet the minimum sample size required to estimate intake at the 90th percentile

VI. BASIS FOR GRAS DETERMINATION

A comprehensive search of the literature for articles on the potential toxicity of green tea and its catechin components was conducted by Morgan Lewis through November 1, 2006. To identify such articles, Medline, Toxline, and The International Bibliographic Information on Dietary Supplements (IBIDS) were searched. Broad search terms were used for the initial searches, which resulted in the identification of about 3,500 abstracts. These abstracts were reviewed for their relevance and validity with respect to safety issues for tea catechins, resulting in the identification of 14 abstracts addressing: (1) pharmacokinetics and bioavailibility; (2) green tea-induced asthma; and (3) mutagenicity.

Articles falling into the following categories were not included: (1) studies evaluating efficacy; (2) clinical studies in populations of diseased patients; (3) pre-clinical studies in genetically-altered mice; (4) studies conducted in a manner inconsistent with FDA's general standards; and (5) in general, studies using only one of the catechins found in Kao's GTC extract.

The following data, including a number of toxicological and metabolic studies, provide a well-documented basis from which to evaluate and document the safety of GTC. Published studies on substantially equivalent GTC extracts, and unpublished studies on Kao's GTC extract, in both animals and humans, provide strong evidence of the safe use of GTC as an additive to beverages for human consumption.

A. Absorption, Distribution, Metabolism and Excretion (ADME)

Epigallocatechin-3-gallate (EGCg), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin are the major green tea catechins (GTC). EGCg comprises 50-60% of green tea catechins.[32]

Absorption of GTC into human plasma was investigated by chemiluminescence (CL)-HPLC in healthy subjects (n=3; non-smokers) who orally ingested 3, 5, or 7 capsules of green tea extract corresponding to 225, 375, and 525 mg EGCg and 7.5, 12.5, and 17.5 mg EGC, respectively.[33] Generally, one tea cup of green tea contains about 100 mg of catechins. Therefore, the total amount of EGCg and EGC provided by 3, 5, and 7 capsules of green tea extract was roughly comparable to that of tea catechins in 2, 4, and 6 cups of green tea, respectively. Ninety minutes after a single oral intake, the plasma EGCg concentrations were significantly increased to 300, 1970, and 2020 ng/mL (657, 4300, and 4410 pmol/mL) in subjects who received 3, 5, and 7 capsules of green tea extract, respectively. The plasma EGC concentrations also were significantly increased to 10, 44, and 78 ng/mL (35, 144, and 255 pmol/mL) in subjects who received 3, 5, and 7 capsules of green tea extract, respectively. Plasma EGCg and EGC levels before administration of

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32 Miyazawa, T., et al., 2000. Absorption and metabolism of natural antioxidants *Kagaku to Seibutu* 38(2) 104-114. [Article in Japanese]

33 Nakagawa, K., et al , 1997 Dose-dependent incorporation of tea catechins, (-)-epigallocatechin-3-gallate and (-)-epigallocatechin into human plasma *Biosci. Biotech Biochem* 61(12) 1981-1985

the green tea extract were below the detection limit of <2 pmol/mL plasma. These results suggested a dose-dependent absorption of EGCg and EGC in their free forms into human plasma. No difference was observed for calculated percentages of absorbed amount against dosage between EGCg (0.2-2%) and EGC (0.2-1.3%). These data may imply that there is no difference in the absorption kinetics of EGCg and EGC.

In another study, EGCg was detected by HPLC-electrochemical detector (ECD) system in the serum of four healthy volunteers who had ingested green tea.[34] Sixty minutes after single oral intake of green tea extract containing 105 mg EGCg, EGCg concentrations in human serum were 30-80 ng/mL (65-175 pmol/mL). The concentration of EGCg in the serum reached the highest level approximately 2 hours after ingestion of green tea, and then decreased. The highest serum concentrations of EGCg ranged from 63 ng/mL to 142 ng/mL. Similarly, mean peak levels of EGCg in plasma samples from 12 healthy volunteers were measured 2 hours after ingestion of single doses of GTC in free or phospholipid complex form (equivalent to 400 mg EGCg), as determined by HPLC with coulometric detector.[35] The mean peak levels of EGCg were 1.84±0.29 μg/mL (4±0.6 μM) and 0.9±0.1 μg/mL (2±0.2 μM) for phospholipid complex and free cathechins, respectively, and decreased slowly to approximately 0 4±0.1 μg/mL at 6 hours. Thus, catechins were absorbed in higher amounts when administered as phospholipid complex, although the percent absorption of EGCg did not exceed 2% of the given dose

In a study using a HPLC-coulochem electrode array detection (CEAS) method, the limits of detection for EGCg, EGC, ECG, and epicatechin ranged from 0.5 ng/mL to 1.5 ng/mL of plasma or urine.[36] One hour after ingestion of 1.2 g of decaffeinated green tea (containing 88, 82, 32, and 33 mg of EGCg, EGC, epicatechin, and ECG, respectively), the plasma samples from four human volunteers contained 46-268 ng/mL (100-585 pmol/mL) EGCg, 82-206 ng/mL EGC, 48-80 ng/mL epicatechin. ECG was not detected in human plasma samples. Plasma EGC was mostly in the glucuronide form (57-71%), followed by the sulfate (23-36%), and the free (3-13%) forms. Plasma epicatechin was exclusively in the conjugated form, with approximately two-thirds sulfate and one-third glucuronide. Plasma EGCg was mostly in the sulfate form (58-72%) followed by the free (12-28%) and glucuronide (8-19%) forms. The maximum urinary excretion of EGC and epicatechin occurred at 3-6 hours after dosing. Most of the EGC and epicatechin was excreted in the first 9 hours. The cumulative urinary excretions in the first 24 hours were 2.8-3.2 mg EGC and 1.6-2.3 mg epicatechin. EGCg and ECG were not detected in the urine samples. The sulfate and glucuronide forms of both EGC and epicatechin were present at approximately a 2:1 ratio. Free EGC was present at <1% of the conjugated form, but free epicatechin was not detected. The ratio of different forms of metabolites did not change in the early and late urine samples. Since plasma EGC was mostly in the glucuronide form and urinary excretion of EGC and epicatechin was mainly in the sulfate forms, it is likely that EGC glucuronide is excreted in the bile, released into

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34 Unno, T., et al., 1996 Analysis of (-)-epigallocatechin gallate in human serum obtained after ingesting green tea *Biosci. Biotech Biochem* 60(12).2066-2068

35 Pietta, P , et al , 1998. Relationship between rate and extent of catechin absorption and plasma antioxidant status *Biochem. Mol Biol Int* 46(5)·895-903.

36 Lee, M , et al , 1995 Analysis of plasma and urinary tea polyphenols in human subjects *Cancer Epidemiol Biomarkers Prev* 4(4) 393-399.

the intestine, and excreted in the feces. The total amount of excreted EGC and epicatechin was approximately 5 mg, accounting for 2% of the total polyphenol ingested. These data suggest that the major elimination pathways of tea polyphenols are via glucuronidation and sulfation.

The pharmacokinetic parameters of GTC have been investigated in several human studies. In one study, 18 healthy volunteers (six subjects per dose level) were given 1.5, 3, and 4.5 g of decaffeinated green tea solids dissolved in 500 mL of water.[37] The plasma concentrations of EGCg, EGC, and epicatechin reached peak levels between 1.5 and 2.5 hours and declined to undetectable levels after 24 hours, as determined by the HPLC-CEAS method. When the dose of decaffeinated green tea solids was increased from 1.5 g to 3 g, the mean maximum concentration (C_{max}) values increased 2.7-fold for EGCg (from 120 to 326 ng/mL), 3.4-fold for EGC (from 148 to 508 ng/mL), and 3.4-fold for epicatechin (from 55 to 189 ng/mL). The higher C_{max} value for EGC than EGCg suggests that EGCg has a lower absorbability or a larger volume of distribution (Vd) than EGC. The mean area under the concentration-time curve (AUC) values, which reflect the extent of absorption, increased 2.5-fold for EGCg (from 897 to 2223 ng/hour/mL), 4-fold for EGC (from 617 to 2493 ng/hour/mL), and 3.8-fold for epicatechin (from 279 to 1059 ng/hour/mL). However, increasing the dose from 3 g to 4.5 g did not further increase C_{max} or AUC values for any of the three catechins, suggesting a saturation phenomenon. The mean time to peak concentration (T_{max}) for EGCg (1.6-2.7 hours) was longer than that for EGC or epicatechin (1.3-1.8 hours). T_{max} values were not affected by the dose increase, suggesting that the dose may not affect the absorption and access of these tea catechins to the bloodstream. The mean half-life ($t_{½}$) values were approximately 5 hours and 2.7 hours for EGCg and EGC, respectively, and were not affected by the dose increase. For epicatechin, the mean $t_{½}$ values decreased at higher doses (from 5.7 to 3.2 hours). Consistent with the data described above, most of the catechins in plasma were in the sulfate- and glucuronide-conjugated forms Over 90% of the total urinary EGC and epicatechin was excreted within 8 hours. After 24 hours, EGC and epicatechin levels in the urine were below the detection limit. Consistent with previous observations, EGCg was not excreted in the urine.

In another human study, the systemic availability of GTC was determined after single oral dose administration of EGCg and Polyphenon E (decaffeinated mixture of EGCg, EGC, epicatechin, and other tea polyphenols) by the HPLC-CEAS method.[38] Twenty healthy volunteers (five subjects per dose level) were randomly assigned to 200, 400, 600, and 800 mg (based on EGCg content) dose levels. All subjects were randomly crossed-over to receive the two catechin formulations at the same dose level. After oral administration, plasma EGCg levels increased toward a peak and declined rapidly, with very low/undetectable levels at 24 hours after dosing. After EGCg *versus* Polyphenon E administration, the mean AUC values of unchanged EGCg at the 200, 400, 600, and 800 mg dose levels were 22.5 *versus* 21.9, 35.4 *versus* 52.2, 101.9 *versus* 79.7, and 167.1 *versus* 161.4 min×μg/mL, respectively. The mean C_{max} values of EGCg were 73.7 ± 25.3, 111.8 ± 98.6, 169.1 ± 139.6, and 438.5 ± 284.4 ng/mL after a 200, 400, 600, and 800 mg dose of EGCg, respectively. Plasma EGCg levels observed after Polyphenon E administration were similar to

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37 Yang, C S , et al , 1998 Blood and urine levels of tea catechins after ingestion of different amount of green tea by human volunteers *Cancer Epidemiol Biomarkers Prev* 7(4).351-354

38 Chow, H.-H S., et al., 2001 Phase I pharmacokinetic study of tea polyphenols following single-dose administration of epigallocatechin gallate and Polyphenol E *Cancer Epidemiol Biomarkers Prev* 10(1).53-58

those seen after EGCg administration, with the mean C_{max} values of 72.7 ± 66.4, 125.3 ± 50.4, 165.7 ± 126.9, and 377.6 ± 149.8 ng/ml at the 200, 400, 600, and 800 mg dose levels, respectively. There were no significant differences in the pharmacokinetic characteristics of EGCg between the two study treatments. The AUC and C_{max} values of EGCg after the 800 mg dose of EGCg were significantly higher than those after the 200 mg and 400 mg doses ($p<0.05$). The AUC and C_{max} values of EGCg after the 800 mg dose of Polyphenon E were significantly higher than those after 200, 400, and 600 mg doses ($p<0.05$). EGC and epicatechin were not detected in plasma after EGCg administration and were present at low/undetectable levels after Polyphenon E administration. High concentrations of EGC and epicatechin glucuronide/sulfate conjugates were found in plasma and urine samples after Polyphenon E administration. EGCg was not detectable in the urine. The systemic availability of EGCg increased at higher doses, possibly due to saturable presystemic elimination of orally administered green tea polyphenols.

In a third study, the pharmacokinetic parameters of GTC were analyzed by the HPLC-CEAS method after administration of a single oral dose of green tea or decaffeinated green tea (20 mg tea solids/kg corresponding to 195 mg EGCg, 154 mg EGC, and 45 mg epicatechin for an individual with a body weight of 70 kg) or EGCg (2 mg/kg) to eight healthy subjects.[39] The peak plasma concentrations of EGCg, EGC, and epicatechin were reached in 1-2 hours in all subjects, and gradually reduced to undetectable levels in 24 hours. The mean C_{max} values of EGCg, EGC, and epicatechin after a single dose of green tea were 77.9 ± 22.2, 223.4 ± 35.2, and 124.03 ± 7.86 ng/mL, respectively, and the corresponding mean AUC values were 508.2 ± 227, 945.4 ± 438.4, and 529.5 ± 244.4 ng×hour×mL^{-1}, respectively. The T_{max} values were in the range of 1.3-1.6 hours. The elimination $t_{½}$ values of EGCg, EGC, and epicatechin were 3.4 ± 0.3, 1.7 ± 0.4, and 2.0 ± 0.4 hours, respectively. At the time point T_{max}, 0.16%, 0.58%, and 1.1% of the ingested doses of EGCg, EGC, and epicatechin from green tea administration were present in the circulating plasma. In the case of decaffeinated green tea administration, the values in the blood were 0.13%, 0.53%, and 0.71%, respectively. When pure EGCg was administered, only 0.1% of the ingested dose appeared in the blood at T_{max} These results indicate that a lower fraction of EGCg than EGC and EC appears in the blood, but the EGCg has a longer $t_{½}$. Considerable interindividual differences and variations in the pharmacokinetic parameters were noted between repeated experiments with green tea, but not when EGCg was given in decaffeinated green tea or in pure form. Consistent with the previous reports, EGCg was mostly present in the free form in the plasma, whereas EGC and epicatechin were mostly in the conjugated form. Most of the conjugated catechins were in the glucuronide form. Over 90% of the total urinary EGC and epicatechin, almost all in the conjugated forms, were excreted during first 8 hours. EGCg was present in trace or undetectable amounts in the urine samples. Substantial amounts of 4'-*O*-methyl EGC metabolite, at levels higher than EGC, were detected in the urine and plasma. The plasma level of 4'-*O*-methyl EGC peaked at 1.7 ± 0.5 hours with a $t_{1/2}$ of 4.4 ± 1.1 hours. It remains to be determined whether the level of 4'-*O*- methyl EGC is influenced by the polymorphism of catechol-*O*-methyl transferase, an enzyme that catalyzes the methylation of EGC.[40,41] Two ring-fission metabolites, (-)-5-(3',4',5'-

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39 Lee, M -J., et al , 2002. Pharmacokinetics of tea catechins after ingestion of green tea and (-)-epigallocatechin-3-gallate by humans. formation of different metabolites and individual variability *Cancer Epidemiol. Biomarkers Prev* 11(10 Pt 1):1025-1032.

40 Weinshilboum, R M , et al , 1999. Methylation pharmacogenetics catechol *O*-methyltransferase, thiopurine methyltransferase, and histamine *N*-methyltransferase. *Annu Rev Pharmacol Toxicol* 39 19-52

trihydroxyphenyl)-γ-valerolactone (M4) and (-)-5-(3',4'-dihydroxyphenyl)-valerolactone (M6), appeared in significant amounts after 3 hours and peaked at 8-15 hours in the urine as well as in the plasma.[42] The levels of urinary M6 (5 ± 2 mg) accounted for 11.2% of the ingested epicatechin. The amount of excreted M4 corresponded to 1.4% of the ingested EGC, the direct precursor of M4.

A comparison of the pharmacokinetic parameters of EGCg from the three studies discussed above is shown in Table 6 below. All human studies demonstrated that only a small percentage (e.g., typically less than 1%) of the orally-ingested catechins appears in the blood. EGC and epicatechin appear to be more bioavailable, but the fractions of these compounds that appeared in the plasma are also low, and only 3.3% and 8.9% of the ingested EGC and epicatechin were excreted in the urine. The presence of substantial amounts of 4'-*O*- methyl EGC, M4, and M6 in the plasma and urine account for some of the ingested catechins.

Table 6. Comparison of the EGCg pharmacokinetics

	Lee et al.[12,a]	Yang et al.[43,b]			Chow et al.[44,c]			
Dose of EGCg (ng)	195	110	220	330	200	400	600	800
T_{max} (hour)	1.6	1.6	2.4	2.7	2.1	1.8	3	4
$t_{½}$ (hour)	3.4	5.5	5	4.9	2	2.7	3.1	1.9
C_{max} (ng/mL)	78	119	326	321	74	112	169	438
AUC (ng×hour/mL)	508	897	2223	2462	367	623	2214	2779

[a] Green tea was used; the data are for EGCg and its conjugates (analyzed together).
[b] Decaffeinated green tea was used; the data are for EGCg and its conjugates (analyzed together).
[c] EGCg tea was used; the data are for EGCg.

Most of the ingested EGCg (i.e., >99%) apparently does not get absorbed into the blood, and the absorbed EGCg (0.1%) is preferentially excreted through the bile to the colon in rats.[45] After intravenous administration of decaffeinated green tea solution (25 mg/kg in saline) to rats, the highest concentration of EGCg was found in the intestine samples, and the intestinal EGCg level declined slowly with an estimated $t_{½}$ of 173 minutes as determined by the HPLC-CEAS method.

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41 Zhu, B T , et al., 2000. *O*-Methylation of tea polyphenols catalyzed by human placental cytosolic catechol-*O*-methyltransferase. *Drug Meta Dispos* 28 1024-1030.

42 Lee, M -J , et al , 2002. Pharmacokinetics of tea catechins after ingestion of green tea and (-)-epigallocatechin-3-gallate by humans. formation of different metabolites and individual variability. *Cancer Epidemiol Biomarkers Prev* 11(10 Pt 1)·1025-1032

43 Yang, C S , et al , 1998 Blood and urine levels of tea catechins after ingestion of different amount of green tea by human volunteers *Cancer Epidemiol Biomarkers Prev.* 7(4)·351-354

44 Chow, H -H S , et al., 2001 Phase I pharmacokinetic study of tea polyphenols following single-dose administration of epigallocatechin gallate and Polyphenol E *Cancer Epidemiol Biomarkers Prev* 10(1) 53-58.

45 Chen, L , et al , 1997 Absorption, distribution, and elimination of tea polyphenols in rats. *Drug Metab Dispos* 25(9)·1045-1050

The highest levels of EGC and epicatechin were observed in the kidney, and the levels declined rapidly with $t_{1/2}$ of 29 minutes and 28 minutes, respectively. Consistent with the observations in the plasma, the $t_{1/2}$ for EGCg was longest among the three tea polyphenols in the tissues examined. The AUC values of EGCg were 1.7, 0.3, and 0 4 mg×min/g in the intestine, kidney, and lung, respectively. The AUC values of EGC were 1.4, 1.2, and 0.9 mg×min/g in the kidney, lung, and intestine, respectively. The AUC values of epicatechin were 0.3, 0.1, and 0.4 mg×min/g in the kidney, lung, and intestine, respectively. Thus, the AUC value of EGCg in the intestine was 4-fold higher than that in the kidney, but the AUC values of EGC and epicatechin in the intestine were similar to those in the kidney. These results suggest that EGCg is excreted mainly through the bile, while EGC and epicatechin are excreted through both the bile and urine. These results are in agreement with the observations in humans, when EGC and epicatechin, but not EGCg, were detected in human urine samples. Low levels of EGCg, EGC, and epicatechin were also detected in the liver. The liver and lung levels of EGCg, EGC, and epicatechin were generally lower than those in the intestine and the kidney.

When EGCg (500 mg/kg body weight in distilled water) was administered orally to rats via gavage, the highest distribution of EGCg was detected by CL-HPLC in the gastrointestinal mucosa, mainly in the small intestine (565 nmol/g), followed by the colon mucosa (68.6 nmol/g), liver (48.4 nmol/g), and plasma (12.3 nmol/g).[46] A very low concentration of EGCg (0.5 nmol/g) was detected in the brain. The direct incorporation of EGCg into the intestinal mucosal cells of a rat that had ingested EGCg was confirmed by CL-HPLC.[47] A specific maximum emission wavelength of 630 nm was detected in small intestinal mucosal cells in rats administered oral EGCg (23 mg/100 g body weight in distilled water). EGCg, EGC, ECG, and epicatechin, administered orally to rats (100 mg each in distilled water), were absorbed into portal blood via the intestinal tract as determined by the HPLC-UV method.[48] When tritium-labeled EGCg ([^{3}H]EGCg) was administered to mice, the radioactivity was detected in various tissues including the gastrointestinal tract, liver, brain, lung, heart, kidney, bone, and skin.[49]

In clinical samples from humans after drinking green tea, EGCg was distributed in plasma, portal blood, bile, stomach mucosa, and large intestinal mucosa as shown in Table 7 below.[50]

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46 Nakagawa, K. and T Miyazawa, 1997. Absorption and distribution of tea catechin, (-)-epigallocatechin-3-gallate, in the rat *J Nutr Sci Vitaminol.* 43:679-684.

47 Miyazawa, T and K Nakagawa, 1998 Structure-related emission spectrometric analysis of the chemiluminescence of catechins, theaflavins and anthocyanins. *Biosci Biotech Biochem* 62(4) 829-832

48 Okushio, K , et al., 1996 Absorption of tea catechins into rat portal vein. *Biol Pharm Bull* 19(2).326-329.

49 Miyazawa, T , et al , 2000 Absorption and metabolism of natural antioxidants *Kagaku to Seibutu* 38(2) 104-114 [Article in Japanese]

50 Miyazawa, T., et al , 2000 Absorption and metabolism of natural antioxidants *Kagaku to Seibutu* 38(2) 104-114 [Article in Japanese]

Table 7. Free EGCg concentration after drinking the green tea catechin EGCg (250 mg) in humans

Tissue	3 hours after ingestion	12 hours after ingestion
Blood plasma (ng/mL)	491±502 (115-1229, n=4)	129±90 (28-268, n=11)
Portal blood (ng/mL)*	527±200 (330-730, n=3)	104±65 (61-201, n=4)
Bile (ng/mL)	68±80 (6-158, n=3)	61±6 (56-65, n=2)
Gastric mucosa (ng/g)	343±127 (167-464, n=4)	111±70 (50-207, n=4)
Large intestinal mucosa (ng/g)	Not analyzed	531±366 (51-1015, n=6)

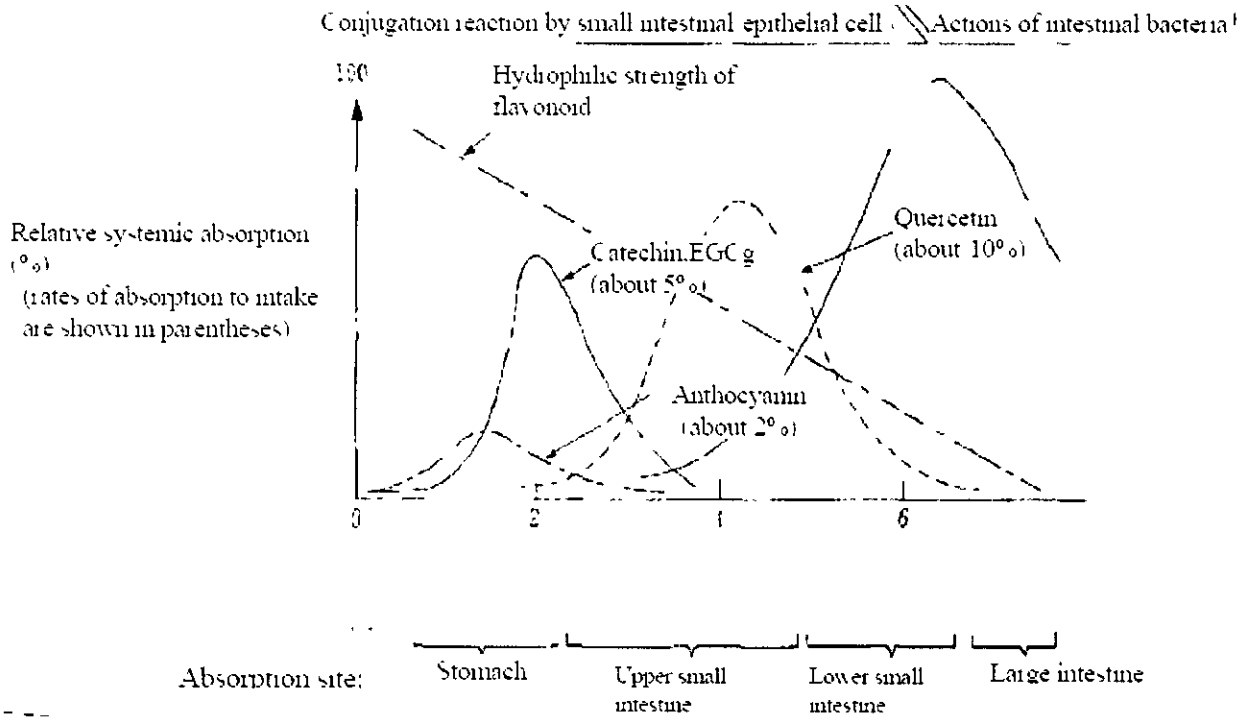
* Venous blood from the right gastroepiploic vein that connects the stomach and portal vein.

However, very large individual variation was noted in the distribution levels. Since the portal blood sample analyzed was venous blood from the right gastroepiploic vein that connects the stomach and portal vein, the detection of EGCg in this sample suggested that a portion of catechins was absorbed from the stomach, in addition to the upper small intestine. This is one of the reasons for the rapid maximum absorption time (time required to reach the maximum blood level after ingestion).

In summary, ingested GTCs are mostly distributed in the gastrointestinal mucosa, and excreted in feces upon detachment from the mucosa.[51] Five to 8% of ingested GTC is absorbed within a relatively short time (probably from the stomach and upper small intestine), and partially conjugated with glucuronide and sulfate in mucoepithelial cells upon absorption. Figures 2 and 3 below provide graphical representations of the absorption and metabolic pathways for various flavonoids, including catechins, respectively.

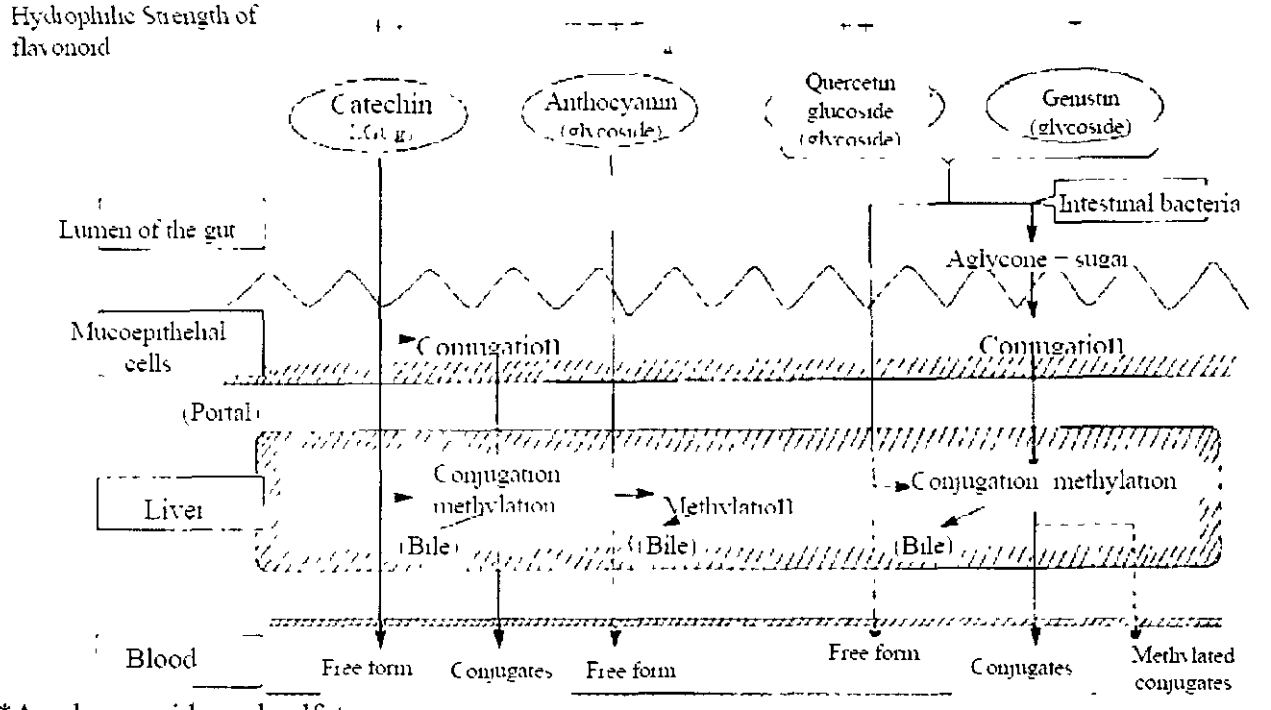
51 Miyazawa, T., et al., 2000 Absorption and metabolism of natural antioxidants *Kagaku to Seibutu* 38(2) 104-114 [Article in Japanese]

Figure 2. Absorption Site, Amount, and Maximum Absorption Time of Major Dietary Flavonoids



*Aglycone production, ring fission, and dehydration reaction by intestinal bacteria.
Source: Miyazawa et al. 2000.

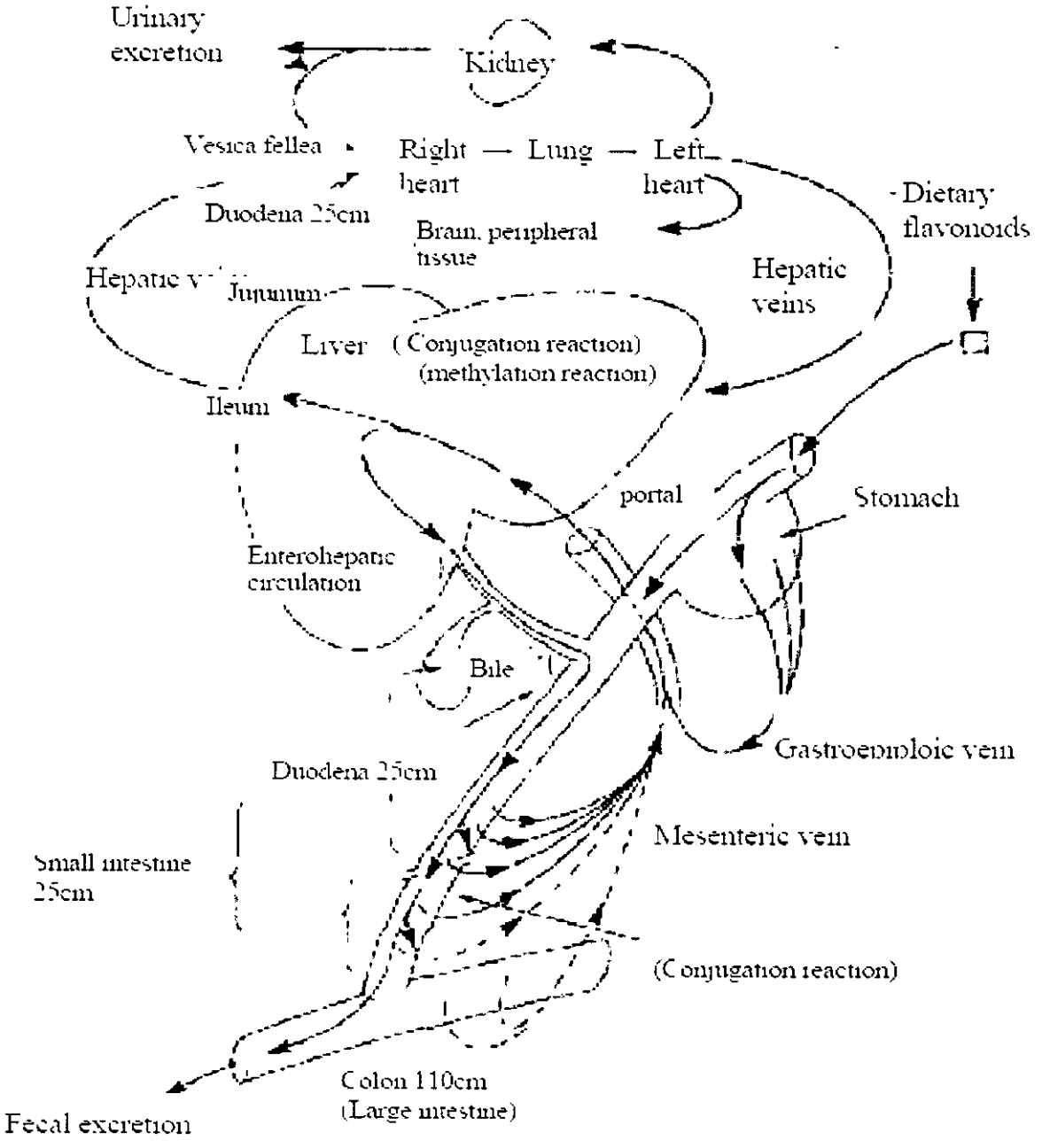
Figure 3. Differences in Conjugation and Methylation due to Dietary Flavonoid Structure



*As glucuronide and sulfate
Source: Miyazawa et al. 2000.

Following absorption, GTC is transported to the liver via the portal system, resulting in the formation of glucuronide, sulfate and/or methyl conjugates. A portion enters blood flow as the free form or conjugates, and is transported to peripheral tissues. Some of the free form and conjugates may be contained in bile secreted by the liver and enter the enterohepatic circulation. Figure 4 below provides a graphic representation of the absorption and metabolism of flavanoids, including catechins.

Figure 4. Absorption and Metabolic Pathway of Dietary Flavanoids



Source: Miyazawa et al. (2000).

Blood catechins are considered to be finally excreted in urine through the kidney. The ratio of the free form:sulfate:glucuronide in human blood changes depending on the catechin intake, is basically determined by the sulfate pool in the body, and is normally 2-3:2-3:1. Compared to other

catechins, EGCg and EGC are less likely to be methylated by liver catechol *O*-methyltransferase, which uses catechol structures as the substrate, because they possess three hydroxyl groups (pyrogallol structure) in the B ring

B. Toxicology Studies

1. Short-term Toxicity Studies of Green Tea Catechin (GTC)

Due to a heat-sterilization step in the manufacture of one type of Green Tea Beverage, many of these studies were conducted in parallel with both a heat-treated ("HT-GTC") and non-heat-treated version of Green Tea Catechin ("UT-GTC"). A number of short-term toxicity studies were conducted on Kao's HT-GTC and UT-GTC. These unpublished studies are summarized in Table 8.

Pages 44-56 have been removed - unpublished information

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4. Toxicology Studies on Substances Similar in Composition to Green Tea Catechin (GTC)

The medical literature contains toxicity studies performed on substances similar in composition (i.e., substantially equivalent) to GTC (e.g., Polyphenon E, Polyphenon 70S, and Polyphenon 30). The relative composition of these related substances are presented below in Table 10. Study results are summarized in Table 11.

Table 10. Catechin and Polyphenol Composition of Related Tea Catechin Products

	Polyphenon 70S	Polyphenon E	Polyphenon 30	Green Tea Catechin (GTC)
Total Catechin Monomers	78.7 %	87.3 %	34.2%	44.4%
Polyphenols	86.4 %	96 7 %	No data	52 9%
Caffeine	0 %	0 %	6.9%	2.6%
Relative Catechin Profile (% of Total Catechin Monomers)				
Gallocatechin (GC)	6.9 %	0.0 %	2.1%	5.4%
Epigallocatechin (EGC)	20.1 %	4.8 %	9 0%	29.8%
Catechin (C)	2.7 %	1.0 %	0.0%	2.0%
Epicatechin (EC)	8.5 %	10 2 %	2.3%	6.8%
Epigallocatechin gallate (EGCG)	42 9 %	74.8 %	17.0%	43 7%
Gallocatechin gallate (GCG)	4 7 %	4.0 %	0.7%	1.1%
Epicatechin gallate (ECG)	12 7 %	4.9 %	2.7%	10.4%
Catechin gallate (CG)	1.5 %	0.0 %	0.4%	1.0%

Table 11. Toxicology Studies on Substances Similar in Composition to Green Tea Catechin (GTC)

Reference	Results of Toxicity study
Matsumoto et al 1999 (Polyphenon 70S)	Green tea extract (Polyphenon 70S) was administered orally to rats for 6 months at levels of 500-2000 mg/kg/day. In rats administered 2000 mg/kg/day, the weight of liver increased, and plasma alkaline phosphatase and GPT levels rose concomitant with a slight degeneration of hepatocytes observed upon histopathological examination. The NOAEL for green tea extract (Polyphenon 70S) was 1000 mg/kg/day.
Faqi et al. 2001 [abstract] (Polyphenon E)	Pregnant Sprague Dawley rats were administered Polyphenon E green tea extract orally by gavage on gestation on gestation days 6-15 at doses of 0, 125, 250, 500, and 1000 mg/kg bw No signs of maternal toxicity were observed in any treatment group, and there was no difference in maternal body and organ weights as compared to the vehicle control group. There was no evidence of developmental toxicity: resorption rates, mean litter size, sex ratio, fetal body weights, and fetal morphology were comparable across all groups. The NOAEL was determined to be 1000 mg/kg bw for developmental toxicity (the highest dose tested)
Chang et al. 2003 (Polyphenon E)	The following assays were conducted. bacterial mutagenesis, mouse lymphoma cell thymidine kinase (TK), gene mutation, the Big Blue CII transgenic mutation (both acute and repeated dose), and the mouse micronucleus assay. • No significant colony revertants were observed in the bacterial assay • A significant increase was observed in the TK assay • Genotoxicity was observed at levels of 2,000 mg/kg-bw/day in mice No significant increases in micronucleated erythrocytes in the bone marrow of Swiss-Webster mice and no significant increases in cII transgene MF in the liver, lung, or spleen were observed at lower doses as compared with controls
Matsumoto et al. 1999 (Polyphenon 30)	A single-dose oral of green tea extract was administered to mice at levels of 3000-6221 mg/kg (in physiological saline), and the animals were observed for 14 days. As a result of the deaths observed at doses of 4320 mg/kg and higher, the oral LD_{50} was estimated to be 4647.29 mg/kg Irritation of the oral mucosa also was assessed in hamster cheek pouches. Three groups of 9-10 animals each were exposed to a negative control (physiological saline), a positive control (sodium lauryl sulfate), and 50% Polyphenon 30 in water for 30 minutes Exposure to Polyphenon 30 resulted in no irritation immediately after or 24 hours after treatment.

C. Human Clinical Studies

A series of short- and long-term clinical investigations examining tolerability and nutritional effects in humans have been conducted with substances highly similar to GTC. In all cases, clinical studies have demonstrated that substances highly similar to GTC are well tolerated, and no toxicological adverse effects were reported as a result of consumption. It is important to note, however, that these studies were primarily conducted to evaluate the potential weight/fat reducing effects of GTC.

1. Published Studies Assessing Safety-related Parameters After Consumption of Substances Highly Similar to Green Tea Catechin (GTC)

Many of the studies assessing the safety of GTC or highly similar substances are published in peer-reviewed journals. Summaries of select published studies are provided in Table 12 below (see next page).

Table 12. Summary of Published Studies Assessing Safety-related Parameters for GTC and Highly Similar Substances[60]

Study	Similarity of Test Substance	Design/ Duration	Subjects	Primary Endpoints	Hematology/ Clinical Chemistry/Other	Results
Nagao, T., et al A Green Tea Extract High in Catchins Reduces Body Fat and Cardiovascular Risks in Humans [*Obesity* in press]	Within 5% of GTC (heat treated) specifications for all catechins	Double-blind, parallel Control group 96 3 GTC mg/day (n=135) Test group 583 GTC mg/day (n=135) 2-week run-in followed by 12-week test period	240 obese males and females (270 enrolled) Mean age 41 7±9 9 years Mean BMI. 26 8±2 0	• Anthropometry (height, body weight, waist circumference, hip circumference, body fat ratio) • Abdominal fat (CT) • Systolic blood pressure (SBP) • Diastolic blood pressure (DBP) • Pulse rate	At baseline and every 4 weeks Clinical chemistry TG, T-CHO, HDL-CHO, LDL-CHO, FFA, plasma glucose, GOT, GPT, γ-GTP, LDH, ALP Hematology. WBC, RBC, Hb, Hct, PLT	• Decreases in body weight, body mass index, body fat ratio, waist circumference, hip circumference, body fat mass, visceral fat area, and subcutaneous fat area were significantly greater in the catechin group as compared to the control group. • For subjects with baseline systolic blood pressures of >130 mmHg, a significant decrease in SBP was observed • LDL-CHO decreased to a significantly greater extent in the catechin group vs. the control group • There were no differences between the groups in any other clinical chemistry or hematology paramter. • No adverse effects were reported by the subjects in this study

60 Abbreviations used in the table: GTC = green tea catechins; TC = tea catechins (type unspecified); TG = triacylglycerol, T-CHO = total cholesterol; HDL-CHO = high-density lipoprotein cholesterol; LDL-CHO = low-density lipoprotein cholesterol; RLP-CHO = remnant-like lipoprotein cholesterol; FFA = free fatty acid, FBG = fasting blood glucose, PAI-1 = total plasminogen activator-1, MDA-LDL = malondialdehyde-modified LDL, BUN = blood urea nitrogen, IP = inorganic phosphate; GOT = glutamic oxalacetic transaminase, GPT = glutamic-pyruvic transaminase; γ-GTP = γ-glutamic-pyruvic transaminase, ALB = albumin; ALP = alkaline phosphatase, LDH = lactate dehydrogenase; TP = thymidine phosphorylase; CRE = creatine, UA = uric acid, WBC = white blood cell count, RBC = red blood cell count, Hb = hemoglobin, Hct = hematocrit; PLT = platelets; PL = phospholipids; MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration; UIBC = unsaturated iron binding capacity, CPK = creatine phosphokinase; AMY = amylase; AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = gamma-glutamyltransferase

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Study	Similarity of Test Substance	Design/ Duration	Subjects	Primary Endpoints	Hematology/ Clinical Chemistry/Other	Results
Nagao, T., et al Ingestion of tea rich in catechins leads to a reduction in body fat and malondialdehyde-modified LDL in men *Am J Clin Nutr* 2005. 81:1-8	Within 2% of GTC (heat treated) specifications for all catechins	Double-blind, parallel 2-week run-in followed by 12-week test period Subjects consumed one 340 mL bottle of control or test beverage per day Control group 21.7 GTC mg per beverage (oolong tea) (n = 18) Test group 689 9 mg GTC per beverage (oolong tea) (n = 17)	35 healthy males Mean age· 36 2 years (24-46 years) Mean weight (control group) 73 8 ± 1 3 kg Mean weight (test group) 73 9 ± 1 8 kg	• Anthropometry (height, body weight, waist and hip circumference, body fat ratio) • Abdominal fat (CT)	At baseline and 12 weeks: Clinical chemistry TG, T-CHO, HDL-CHO, LDL-CHO, RLP-CHO, FFA, total ketone body, FBG, insulin, PAI-1, leptin, Vitamin A, BUN, Vitamin E, MDA-LDL, Ca, Fe, IP, Na, K, Cl	• Body weight, BMI, waist circumference, body fat mass, and subcutaneous fat area were significantly lower in the test group • Changes in MDA-LDL were positively associated with changes in body fat mass and total fat area in the test group • No other significant differences in clinical chemistry parameters • Occupational health physician assessments conducted every four weeks reported "no side effects related to the study."
Tsuchida, T , et al. Reduction in body fat in humans by long-term ingestion of catechins. *Progress in Medicine* 2002 26(11).1459-1464	Within 4% of GTC (heat treated)specifications for all catechins	Double-blind, parallel 24 weeks (dosed for 12 weeks, wash-out for 12 weeks) Subjects consumed one 340 mL bottle of control or test beverage per day Control group· 126 mg GTC per beverage (green tea-like drink) Test group 588 mg GTC per beverage (green tea-like drink)	Control group 41 male; 23 postmenopausal females Test group: 39 male, 20 postmenopausal females Mean age (male) 42 1 years (combined groups) Mean age (female): 54.8 years (combined groups) Mean BMI	• Diet diary (3 days/ wk at week 0, 12, and 24) • Anthropometry (every 4 weeks): height, body weight, waist circumference, hip circumference, waist/hip ratio, body fat ratio • Abdominal fat (CT) (Weeks 0, 12, and 24)	Weeks 0, 8, 12, 20, and 24 Clinical Chemistry. TG, T-CHO, HDL-CHO, LDL-CHO, FFA, PL, GOT, GPT, γ-GTP, TP, ALB, CRE, BUN, LDH, ALP, FBG, PAI-1, Na, K, Ca, Cl, IP, magnesium, Fe Hematology: WBC, RBC, Hb, Hct, PLT Urinalysis:	• Body weight, BMI, body fat ratio, waist circumference, hip circumference, and body fat mass were all significantly lower in the test group than baseline and control, waist/hip ratio was significantly higher in the test group compared to baseline and control • Total abdominal body fat, visceral body fat, and subcutaneous body fat were all significantly reduced in the test group compared to baseline and control • No significant differences between groups were observed for any hematologic, circulatory (pulse and diastolic blood pressure), or urinalysis parameter

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Study	Similarity of Test Substance	Design/ Duration	Subjects	Primary Endpoints	Hematology/ Clinical Chemistry/Other	Results
		Caffeine 81-83 mg GTC in each beverage	(male): 26 5 (combined groups) Mean BMI (female) 25.9 (combined groups)		glucose, protein, urobilinogen, ketone body, and protein, sediments if protein was positive Circulatory Pulse, diastolic blood pressure Daily diary	• Significant changes in TG, FFA, and ALB were observed between groups at various time points, but were not considered to be test-article-related because the values were not different from respective baselines • Interviews with subjects "showed no subject complaints of a poor physical condition due to the intake of the test beverage"
Otsuka, K , et al Effects of tea catechins on body fat metabolism in women *Jap J Nutritional Assessment*. 2001 19(3) 365-76	Within 4% of GTC (heat-treated) specifications for all catechins	Double-blind, parallel 8 weeks Daily meals and exercise maintained; alcohol ingestion limited Control group· 9.7 mg/100 mL TC in 340 mL oolong tea beverage (33 mg TC per day) Test group· 163 3 mg/100 mL TC in 340 mL oolong tea beverage (562 mg TC/day) Caffeine concentration kept constant	40 women (19-21 per group) Age 22-53 years	At baseline and every 4 weeks • Anthropometry (body weight, waist circumference, hip circumference) • CT (abdominal fat)	At baseline and 8 weeks: Blood chemistry· TG, T-CHO, HDL-CHO, LDL-CHO, FFA, acetoacetic acid, 3-hydroxybutyric acid, total ketonic acid, AMY, ALP, insulin, FBG, TP, ALB, γ-GTP, GOT, GOT, LDH, BUN, CRE, UA, Fe, Ca, Mg, Na, K, IP, Cl Hematology: WBC, RBC, Hb, Hct, MCV, MCH, MCHC, PLT, UIBC	• No significant differences between groups in any anthropometric measurement • Statistically significant differences in test group compared to baseline values. waist circumference at 4 and/or 8 weeks, waist/hip ratio, total body fat area, and visceral fat area. • When stratified into subjects with BMI< 22 or ≥22, test group exhibited significantly lower total fat and visceral fat areas when compared to controls • No clinically significant changes in blood parameters were observed between groups. • No "study-related poor physical condition" reported
Nagao, T , et al Tea catechins suppress accumulation of body	Experiment 1 Within 7% of	Double-blind, parallel	Experiment 1: 27 healthy males (8-10 per	At baseline and 12 weeks	At baseline and 12 weeks:	• Significant decreases in body weight and BMI observed in 900 mg group compared to control group

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Study	Similarity of Test Substance	Design/ Duration	Subjects	Primary Endpoints	Hematology/ Clinical Chemistry/Other	Results
fat in humans. *J. Oleo Sci* 2001 50(9)·35.	GTC (heat treated) specifications for all catechins Experiment 2 Within 13% of GTC (heat treated) specifications for all catechins Experiment 3. Within 3% of GTC (heat treated) specifications for all catechins	12 or 20 weeks Subjects consumed one 340 mL bottle of control or test beverage per day Control group: 101.5 mg TC per oolong or green tea beverage 600 mg test group 555.4 mg TC in oolong tea beverage 900 mg group B: 901.9 mg TC in oolong tea beverage Subjects instructed to "maintain usual food intake and constant exercise;" alcohol ingestion restricted; maintain diet diary	group) Age: 26-52 years Mean BMI: 25-25 2 Experiment 2 17 healthy males (8-9 per group) Age 25-48 years Mean BMI 3.5-24 4 Experiment 3. 38 healthy males Age: 24-49 years Mean BMI. 24.3-34.6	• Anthropometry (body weight, waist circumference, body fat ratio) • CT (abdominal fat)	Blood chemistry TG, T-CHO, PL, FBG, insulin, GOT, GPT, γ-GTP, AMY, BUN, Vitamin A, Vitamin E, Na, K, Ca, Cl, IP, Fe Hematology· WBC, RBC, Hb, Hct, and PLT	(1 2±1 0%, vs 0 0±0 0 6%, p=0 0440) • Significant decrease in skinfold thickness (body fat ratio) compared to control in 900 mg group (15.1±3 3% versus 2.6±4 5%, p=0 015) • Significant decreases compared to control in total fat area (900 mg group 13.8±3.6% vs 0.7±3 8%, p=0 0142), visceral fat area (600 mg and 900 mg groups 10 7±2.3% and 13 0±4 0%, respectively vs a gain of 12 5±8 5%, p=0.0317 and p=0.0098, respectively), no change in subcutaneous fat area • No significant changes in any hematologic or clinical chemistry parameters • No "study-related poor physical condition" reported
Chow, H H., et al. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigaallocatchin gallate and polyphenon E in	Refer to composition of Polyphenon E in Table 9 above	Five groups (8 subjects/group)· 800 mg EGCG once daily; 400 mg ECGC twice daily; 1070 mg of Polyphenon E (800 mg ECGC) once	40 healthy subjects (8 subjects/group) Between 2 and 4 males in each group Mean age 34 5 ± 10 6 years (control), 39 5 ±	• Adverse event reports • Pharmacokinetics • Blood chemistry	At weeks 0 and 4: Hematology WBC and RBC Clinical Chemistry TG, T-CHO, HDL-CHO, LDL-CHO, FFA, ALP, total protein, total	• All reported events (including excess gas, upset stomach, nausea, heartburn, stomach ache, abdominal pain, dizziness, headache, and muscle pain) were mild and not different in frequency and kind from placebo • No significant differences in hematologic or clinical chemistry

000063

Study	Similarity of Test Substance	Design/ Duration	Subjects	Primary Endpoints	Hematology/ Clinical Chemistry/Other	Results
healthy individuals *Clin Cancer Res.* 2003 9 3312-19.		daily; 535 mg of Polyphenon E (400 mg ECGC) twice daily; and placebo 2-week placebo run in and 4 weeks of treatment with blood collections at Treatment Day 1 and 4 weeks later	10.4 (800 mg EGCG once daily), 32.4 ± 10.1 years (Polyphenon E once daily); 29 4 ± 10.7 years (400 mg EGCG twice daily); and 34.1 ± 11 9 years (Polyphenon E twice daily) Mean weight. 169 ± 36 pounds (control); 165 ± 52 pounds (800 mg EGCG once daily); 167 ± 30 pounds (Polyphenon E once daily); 160 ± 40 pounds (400 mg EGCG twice daily), and 150 ± 19 pounds (Polyphenon E twice daily)		bilirubin, globulin, FBG, ALB, AST, ALT, GGT, LDH, BUN, CRE, UA, Fe, Ca, Na, K, IP, Cl	parameters compared to placebo • AUC differed significantly in the 800 mg Polyphenon E group compared to the 400 mg Polyphenon E group only after 4 weeks repeated administration • C_{max}, T_{max}, and $t_{½}$ not significantly different after repeat administration

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D. Potential Interactions Between Green Tea Catechin and Marketed Drugs

Green tea has been reported to modulate activation and detoxification enzymes. This affect on detoxification enzymes raises the possibility of altering the efficacy or toxicity of marketed drugs, which these enzymes are responsible for metabolizing. *In vitro* and animal studies suggest that green tea catechins modulate expression and activation of certain members of the cytochrome P450 ("CYP") family. In contrast, recent studies in humans show that repeated administration of green tea catechins do not influence the activation of clinically significant enzyme family members – that is, those which are known to be responsible for the metabolism of the vast majority of drugs in the marketplace. Accordingly, current evidence supports the conclusion that green tea catechins do not affect clinically significant CYP enzymes.

Multiple *in vitro* studies provide evidence for the induction of CYP enzymes by green tea catechins -- primarily induction of CYP1A1. For example, Yang and colleagues investigated the affect of green tea extract on mRNA expression levels of CYPs 1A1, 1A2, 2C, 2E1, 2D6, and 4F3. Of these, only CYP1A1 and CYP1A2 showed an increase in mRNA expression.[61] Similarly, Williams et al. showed that modulation of CYP1A1 expression is dependent on multiple components of the extract, rather than merely ECGC alone.[62] Evidence from a recent study by Netsch and colleagues suggests that green tea catechins modulate the expression of drug-metabolizing enzymes, but non-specifically inhibit the function of CYP family members.[63]

In addition to these *in vitro* data, other studies have assessed the potential to modulate the expression of CYP enzymes in animals. Maliakal et al. administered green tea or green tea extract to Wistar rats and observed an increase in both CYP1A1 and CYP1A2 expression.[64] In another study, increased apoprotein levels of CYP1A1 and CYP4A1 were observed following administration of green tea to rats.[65] Sohn and colleagues showed that consumption of green tea by rats led to significant increases in the liver of rats drinking green or black tea of CYP1A1, 1A2 and 2B1 activities, but no change in CYP2E1 and 3A4 activities.[66]

Notwithstanding the *in vitro* and animal evidence suggesting a modulatory effect of green tea catechins on the expression and activity of CYP enzymes, recent studies in humans provide strong evidence against the assertion that co-administration of green tea catechins could alter the metabolism and toxicity of marketed drugs. Chow and colleagues administered green tea catechins

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61 Yang, S P. and G.M Raner, 1998 Cytochrome P450 expression and activivties in human tongue cells and their modulation *Toxicol Appl Pharmacol* 202(2) 140-50.

62 Williams, S.N., et al , 2003 A combination of tea (*Camellia Sinesis*) catechins is required for optimal inhibition of induced CYP1A1 expression by green tea extract *J Agric Food Chem* 51(22) 6627-34.

63 Netsch, M I , et al , 2006. Induction of CYP1A1 by green tea extract in human intestinal cell lines *Planta Med* 72(6):514-20

64 Maliakal, P P , et. al., 2001 Tea consumption modulates hepatic drug metabolizing enzymes in Wistar rats *J Pharm Pharmacol* 53·569-77

65 Bu-abbas, A , et al , 1994 Selective induction of rat hepatic CYP1 and CYP4 proteins and of perixisomal proliferation by green tea. *Carcinogenesis* 15·2575-9

66 Sohn, O S , et al , 1994 Effects of green tea and black tea on hepatic xenobiotic metabolizing systems in the male F344 rat *Xenobiotica* 24.119-27

and a cocktail of probe drugs to 42 healthy volunteers to assess the activity of CYP1A2, 2D6, CYP2C9, and CYP3A4.[67] As noted by the authors, these CYP family members were selected because they account for the metabolism of the majority of medications currently on the market and have been the cause of clinically significant interactions with drugs metabolized by these enzymes. Following repeated administration of 4 weeks, the subjects showed no alteration in the activity of CYP1A2, CYP12D6, and CYP12C9, but a small reduction in CYP3A4 activity was observed. Other recent studies in humans are consistent with these results.[68]

In summary, the data suggesting an interaction between CYP enzymes and marketed drugs are limited to *in vitro* and animal studies. Recent studies in humans do not support a conclusion that green tea catechins may alter the efficacy and toxicity of marketed drugs. In fact, many of these studies conclude that alteration of activity of these enzymes may be providing a protective effect against metabolism-dependent activation of carcinogens. Consequently, it is unlikely that GTC will present a concern with respect to drug interations.

E. Reports that May Appear Inconsistent

In the period between its release in May 2003 and June 2006, Kao sold 614 million bottles of Green Tea Catechin drinks in Japan. During this sales period, Kao received 945 reports of consumer complaints from Green Tea Catechin drink consumers. Most of these cases concerned minor, transient events, such as stomach aches, nausea, diarrhea, constipation, insomnia, and frequent urination. To date, based on medical confirmation, in no case has a connection clearly been established between any reported adverse events and Green Tea Catechin. Apart from these cases, there also has been a small number of cases reporting cutaneous symptoms and hypoglycemia, although no causal relationship to Green Tea Catechin could be established. Kao has confirmed recovery or remission in each of these events, and will continue to diligently monitor these issues.

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67 Chow, H.H., et al , 2006 Effects of repeated green tea catechin administration on human cytochrome P450 activity *Cancer Epidemiol Biomarkers Prev.* 15(12):2473-6

68 See, e g , Donovan, J L., et. al, 2004. Green tea (Camellia sinensis) extract does not alter cytochrome P450 3A4 or 2D6 activity in healthy volunteers *Drug Metab Dispos* 32(9) 906-8. (assessing reponse in 11 individuals)

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Appendix A

Bottled Tea

92301000	TEA, NS AS TO TYPE, UNSWEETENED	Bottled Tea
92301060	TEA, NS AS TO TYPE, PRESWEETENED W/ SUGAR	Bottled Tea
92301080	TEA, PRESWEETENED W/ LOW CALORIE SWEETENER	Bottled Tea
92301100	TEA, NS AS TO TYPE, DECAFFEINATED, UNSWEETENED	Bottled Tea
92301130	TEA, NS AS TO TYPE, PRESWEETENED, NS AS TO SWEETNER	Bottled Tea
92301160	TEA, DECAFFEINATED, W/ SUGAR, NFS	Bottled Tea
92301180	TEA, DECAFFEINATED, LOW CALORIE SWEETENER, NFS	Bottled Tea
92301190	TEA, PRESWEETENED, NS SWEETENER, DECAFFEINATED	Bottled Tea

Appendix B

Sports Drinks

92553000	FRUIT-FLAVORED THIRST QUENCHER BEVERAGE, LOW CAL	Sports drink
92560000	FRUIT-FLAVORED THIRST QUENCHER BEVERAGE	Sports drink
92582050	FRUIT-FLAVORED DRINK, VITAMIN & MINERAL FORTIFIED	Sports drink?

Appendix C

Carbonated Beverages and Juice Drinks

11551050	MILK FRUIT DRINK (INCL LICUADO)	Carb bevs/juices
11552200	MILK-BASED FRUIT DRINK (INCL ORANGE JULIUS)	Carb bevs/juices
11553000	FRUIT SMOOTHIE DRINK, W/ FRUIT AND DAIRY PRODUCTS	Carb bevs/juices
11553100	FRUIT SMOOTHIE DRINK, NOT FURTHER SPECIFIED	Carb bevs/juices
61200500	ACEROLA JUICE	Carb bevs/juices
61201000	GRAPEFRUIT JUICE, NFS	Carb bevs/juices
61201020	GRAPEFRUIT JUICE, UNSWEETENED, NS AS TO FORM	Carb bevs/juices
61201220	GRAPEFRUIT JUICE, CANNED, BOTTLED, CARTON, UNSWEET	Carb bevs/juices
61201230	GRAPEFRUIT JUICE, CANNED, BOTTLED, CARTON, W/ SUGAR	Carb bevs/juices
61201240	GRAPEFRUIT JUICE, CANNED/BOTTLE/CARTON, W/ LOW CAL SWEETENER	Carb bevs/juices
61204000	LEMON JUICE, NS AS TO FORM	Carb bevs/juices
61204200	LEMON JUICE, CANNED OR BOTTLED	Carb bevs/juices
61207000	LIME JUICE, NS AS TO FORM	Carb bevs/juices
61207200	LIME JUICE, CANNED OR BOTTLED	Carb bevs/juices
61210000	ORANGE JUICE, NFS	Carb bevs/juices
61210220	ORANGE JUICE, CANNED/BOTTLED/CARTON, UNSWEETENED	Carb bevs/juices
61210230	ORANGE JUICE, CANNED/BOTTLED/CARTON, W/ SUGAR	Carb bevs/juices
61210250	ORANGE JUICE, W/ CALCIUM, CAN/BOTTLE/CARTON, UNSWEETENED	Carb bevs/juices
61213000	TANGERINE JUICE, NFS	Carb bevs/juices
61214000	GRAPE-TANGERINE-LEMON JUICE	Carb bevs/juices
61219000	ORANGE & BANANA JUICE	Carb bevs/juices
61219100	PINEAPPLE-ORANGE-BANANA JUIICE	Carb bevs/juices
61219150	ORANGE-WHITE GRAPE-PEACH JUICE	Carb bevs/juices

61219650	APRICOT-ORANGE JUICE	Carb bevs/juices
61222000	PINEAPPLE-GRAPEFRUIT JUICE, NFS	Carb bevs/juices
61225000	PINEAPPLE-ORANGE JUICE, NFS	Carb bevs/juices
61226000	STRAWBERRY-BANANA-ORANGE JUICE	Carb bevs/juices
64100100	FRUIT JUICE, NFS (INCLUDE MIXED FRUIT JUICES)	Carb bevs/juices
64100110	FRUIT JUICE BLEND, 100% JUICE, W/ VITAMIN C	Carb bevs/juices
64100120	AMBROSIA JUICE (INCL KNUDSEN'S)	Carb bevs/juices
64101010	APPLE CIDER (INCLUDE CIDER, NFS)	Carb bevs/juices
64104010	APPLE JUICE	Carb bevs/juices
64104050	APPLE JUICE, W/ ADDED VITAMIN C	Carb bevs/juices
64104090	APPLE JUICE WITH ADDED VITAMIN C AND CALCIUM	Carb bevs/juices
64104150	APPLE-CHERRY JUICE	Carb bevs/juices
64104200	APPLE-PEAR JUICE	Carb bevs/juices
64104450	APPLE-RASPBERRY JUICE	Carb bevs/juices
64104500	APPLE-GRAPE JUICE	Carb bevs/juices
64104550	APPLE-GRAPE-RASPBERRY JUICE	Carb bevs/juices
64104600	BLACKBERRY JUICE (INCL BOYSENBERRY JUICE)	Carb bevs/juices
64105400	CRANBERRY JUICE, UNSWEETENED	Carb bevs/juices
64105500	CRANBERRY-WHITE GRAPE JUICE MIXTURE, UNSWEETENED	Carb bevs/juices
64116010	GRAPE JUICE, NS AS TO ADDED SWEETENER	Carb bevs/juices
64116020	GRAPE JUICE, UNSWEETENED	Carb bevs/juices
64116030	GRAPE JUICE, W/ SUGAR	Carb bevs/juices
64116040	GRAPE JUICE, LOW CALORIE SWEETENER	Carb bevs/juices
64116050	GRAPE JUICE, NS AS TO SWEETENED, W/ ADDED VITAMIN C	Carb bevs/juices
64116100	GRAPE JUICE, UNSWEETENED, W/ ADDED VITAMIN C	Carb bevs/juices
64116150	GRAPE JUICE, W/ SUGAR, W/ ADDED VITAMIN C	Carb bevs/juices
64120010	PAPAYA JUICE	Carb bevs/juices

64121000	PASSION FRUIT JUICE	Carb bevs/juices
64122030	PEACH JUICE, W/ SUGAR	Carb bevs/juices
64123000	PEAR-WHITE-GRAPE-PASSION FRUIT JUICE,W/ADDED VIT C	Carb bevs/juices
64124010	PINEAPPLE JUICE, NS AS TO SWEETENED	Carb bevs/juices
64124020	PINEAPPLE JUICE, UNSWEETENED	Carb bevs/juices
64124030	PINEAPPLE JUICE, W/ SUGAR	Carb bevs/juices
64124060	PINEAPPLE JUICE, UNSWEETENED, W/ VIT C	Carb bevs/juices
64124200	PINEAPPLE-APPLE-GUAVA JUICE, W/ ADDED VITAMIN C	Carb bevs/juices
64125000	PINEAPPLE JUICE-NON-CITRUS JUICE BLEND, UNSWEETENED	Carb bevs/juices
64132010	PRUNE JUICE, NS AS TO ADDED SWEETENER	Carb bevs/juices
64132020	PRUNE JUICE, UNSWEETENED	Carb bevs/juices
64132030	PRUNE JUICE, W/ SUGAR	Carb bevs/juices
64132500	STRAWBERRY JUICE	Carb bevs/juices
64133100	WATERMELON JUICE	Carb bevs/juices
64134000	FRUIT SMOOTHIE DRINK, W/ FRUIT ONLY	Carb bevs/juices
64200100	FRUIT NECTAR, NFS	Carb bevs/juices
64201010	APRICOT NECTAR	Carb bevs/juices
64201500	BANANA NECTAR	Carb bevs/juices
64202010	CANTALOUPE NECTAR	Carb bevs/juices
64203020	GUAVA NECTAR	Carb bevs/juices
64204010	MANGO NECTAR	Carb bevs/juices
64205010	PEACH NECTAR	Carb bevs/juices
64210010	PAPAYA NECTAR	Carb bevs/juices
64213010	PASSION FRUIT NECTAR	Carb bevs/juices
64215010	PEAR NECTAR	Carb bevs/juices
64221010	SOURSOP (GUANABANA) NECTAR	Carb bevs/juices
73105010	CARROT JUICE	Carb bevs/juices

74301100	TOMATO JUICE	Carb bevs/juices
74301150	TOMATO JUICE, LOW SODIUM	Carb bevs/juices
74302000	TOMATO JUICE COCKTAIL	Carb bevs/juices
74303000	TOMATO & VEGETABLE JUICE, MOSTLY TOMATO (INCL V-8)	Carb bevs/juices
74303100	TOMATO & VEGETAGLE JUICE, MOSTLY TOMATO, LOW SODIUM	Carb bevs/juices
74304000	TOMATO JUICE W/ CLAM OR BEEF JUICE	Carb bevs/juices
75132000	MIXED VEGETABLE JUICE (OTHER THAN TOMATO)	Carb bevs/juices
75132100	CELERY JUICE	Carb bevs/juices
75200700	ALOE VERA JUICE	Carb bevs/juices
92400000	SOFT DRINK, NFS	Carb bevs/juices
92400100	SOFT DRINK, NFS, SUGAR-FREE	Carb bevs/juices
92410110	CARBONATED WATER,SWEETEND(INCL TONIC,QUININE WATER)	Carb bevs/juices
92410210	CARBONATED WATER, UNSWEETENED (INCL CLUB SODA)	Carb bevs/juices
92410250	CARBONATED WATER, SUGAR-FREE	Carb bevs/juices
92410300	SOFT DRINK, COLA, W/ HIGHER CAFFEINE, SUGAR-FREE (INCL JOLT)	Carb bevs/juices
92410310	SOFT DRINK, COLA-TYPE	Carb bevs/juices
92410320	SOFT DRINK, COLA-TYPE, SUGAR-FREE	Carb bevs/juices
92410330	SOFT DRINK, COLA-TYPE, W/ HIGHER CAFFEINE (INCL JOLT)	Carb bevs/juices
92410340	SOFT DRINK, COLA-TYPE, DECAFFEINATED	Carb bevs/juices
92410350	SOFT DRINK, COLA-TYPE, DECAFFEINATED, SUGAR-FREE	Carb bevs/juices
92410360	SOFT DRINK, PEPPER-TYPE (INCL DR PEPPER, MR PIBB)	Carb bevs/juices
92410370	SOFT DRINK, PEPPER-TYPE, SUGAR-FREE	Carb bevs/juices
92410390	SOFT DRINK, PEPPER-TYPE, DECAFFEINATED	Carb bevs/juices
92410400	SOFT DRINK, PEPPER-TYPE, DECAFFEINATED, SUGAR-FREE	Carb bevs/juices
92410410	CREAM SODA	Carb bevs/juices
92410420	CREAM SODA, SUGAR-FREE	Carb bevs/juices
92410510	SOFT DRINK, FRUIT-FLAVORED, CAFFEINE FREE	Carb bevs/juices

92410520	SOFT DRINK, FRUIT-FLAV, SUGAR-FREE, CAFFEINE FREE	Carb bevs/juices
92410550	SOFT DRINK, FRUIT-FLAVORED, W/ CAFFEINE	Carb bevs/juices
92410560	SOFT DRINK, FRUIT-FLAVORED, W/ CAFFEINE, SUGAR-FREE	Carb bevs/juices
92410610	GINGER ALE	Carb bevs/juices
92410620	GINGERALE, SUGAR-FREE	Carb bevs/juices
92410710	ROOT BEER	Carb bevs/juices
92410720	ROOT BEER, SUGAR-FREE	Carb bevs/juices
92410810	CHOCOLATE-FLAVORED SODA	Carb bevs/juices
92410820	CHOCOLATE-FLAVORED SODA, SUGAR-FREE	Carb bevs/juices
92411510	COLA W/ FRUIT OR VANILLA FLAVOR	Carb bevs/juices
92411520	COLA W/ CHOCOLATE FLAVOR	Carb bevs/juices
92411610	COLA W/ FRUIT OR VANILLA FLAVOR, SUGAR-FREE	Carb bevs/juices
92411620	COLA W/ CHOC FLAVOR, SUGAR FREE	Carb bevs/juices
92416010	MAVI DRINK	Carb bevs/juices
92417010	SOFT DRINK, ALE TYPE (INCLUDE ALE-8)	Carb bevs/juices
92431000	CARBONATED JUICE DRINK, NS AS TO TYPE OF JUICE	Carb bevs/juices
92432000	CARBONATED CITRUS JUICE DRINK	Carb bevs/juices
92433000	CARBONATED NONCITRUS JUICE DRINK	Carb bevs/juices
92510110	APPLE DRINK	Carb bevs/juices
92510120	APPLE-CHERRY DRINK	Carb bevs/juices
92510150	APPLE JUICE DRINK	Carb bevs/juices
92510170	APPLE-CRANBERRY-GRAPE JUICE DRINK	Carb bevs/juices
92510200	APPLE-ORANGE-PINEAPPLE JUICE DRINK	Carb bevs/juices
92510220	APRICOT-PINEAPPLE JUICE DRINK	Carb bevs/juices
92510310	BANANA-ORANGE DRINK	Carb bevs/juices
92510410	BLACK CHERRY DRINK	Carb bevs/juices
92510610	FRUIT DRINK (INCLUDE FRUIT PUNCH & FRUIT ADE)	Carb bevs/juices

92510630	FRUIT JUICE DRINK, NFS	Carb bevs/juices
92510650	TAMARIND DRINK, P R (REFRESCO DE TAMARINDO)	Carb bevs/juices
92510720	FRUIT PUNCH, MADE W/ FRUIT JUICE & SODA	Carb bevs/juices
92510730	FRUIT PUNCH, MADE W/ SODA, FRUIT JUICE & SHERBET	Carb bevs/juices
92510810	GRAPEADE & GRAPE DRINK	Carb bevs/juices
92510820	GRAPE JUICE DRINK	Carb bevs/juices
92510910	GRAPEFRUIT JUICE DRINK	Carb bevs/juices
92510950	GUAVA JUICE DRINK	Carb bevs/juices
92511010	LEMONADE	Carb bevs/juices
92511020	LEMON-LIMEADE	Carb bevs/juices
92511110	LIMEADE	Carb bevs/juices
92511190	ORANGE JUICE DRINK	Carb bevs/juices
92511200	ORANGE-MANGO JUICE DRINK	Carb bevs/juices
92511220	ORANGE DRINK (INCLUDE ORANGE ADE, YABA DABA DEW)	Carb bevs/juices
92511230	ORANGE-APRICOT JUICE DRINK	Carb bevs/juices
92511240	ORANGE-LEMON DRINK	Carb bevs/juices
92511250	CITRUS FRUIT JUICE DRINK (INCL 5-ALIVE)	Carb bevs/juices
92511260	ORANGE-CRANBERRY JUICE DRINK	Carb bevs/juices
92511270	ORANGE-PEACH JUICE DRINK	Carb bevs/juices
92511280	ORANGE-GRAPE-BANANA JUICE DRINK	Carb bevs/juices
92511290	PAPAYA JUICE DRINK	Carb bevs/juices
92511310	PINEAPPLE-GRAPEFRUIT JUICE DRINK	Carb bevs/juices
92511340	PINEAPPLE-ORANGE JUICE DRINK	Carb bevs/juices
92511350	ORANGE-RASPBERRY JUICE DRINK	Carb bevs/juices
92511400	RASPBERRY-FLAVORED DRINK	Carb bevs/juices
92511510	STRAWBERRY-FLAVORED DRINK	Carb bevs/juices
92512090	PINA COLADA, NONALCOHOLIC	Carb bevs/juices

92512110	WHISKEY SOUR, NONALCOHOLIC (INCL LEMIX)	Carb bevs/juices
92520410	FRUIT DRINK, LOW CALORIE	Carb bevs/juices
92520810	GRAPE DRINK, LOW CALORIE	Carb bevs/juices
92520910	LEMONADE, LOW CALORIE	Carb bevs/juices
92530110	APPLE DRINK W/ VITAMIN C ADDED	Carb bevs/juices
92530210	BLACK CHERRY DRINK W/ VITAMIN C ADDED	Carb bevs/juices
92530310	CHERRY DRINK W/ VITAMIN C ADDED	Carb bevs/juices
92530410	CITRUS DRINK W/ VITAMIN C ADDED	Carb bevs/juices
92530510	CRANBERRY JUICE DRINK W/VIT C ADDED(INCL COCKTAIL)	Carb bevs/juices
92530520	CRANBERRY-APPLE JUICE DRINK W/ VITAMIN C ADDED	Carb bevs/juices
92530610	FRUIT PUNCH/DRINK/ADE W/ VIT C ADDED (INCL HI-C)	Carb bevs/juices
92530710	GRAPE DRINK W/ VITAMIN C ADDED	Carb bevs/juices
92530810	GRAPEFRUIT JUICE DRINK W/ VITAMIN C ADDED	Carb bevs/juices
92530840	GUAVA JUICE DRINK W/ VIT C ADDED	Carb bevs/juices
92530910	LEMONADE W/ VITAMIN C ADDED	Carb bevs/juices
92530950	VEGETABLE & FRUIT JUICE DRINK, W/ VIT C	Carb bevs/juices
92531010	ORANGE DRINK & ORANGEADE W/ VITAMIN C ADDED	Carb bevs/juices
92531030	ORANGE BREAKFAST DRINK	Carb bevs/juices
92531110	PINEAPPLE-GRAPEFRUIT JUICE DRINK W/ VIT C ADDED	Carb bevs/juices
92531120	PINEAPPLE-ORANGE JUICE DRINK W/ VITAMIN C ADDED	Carb bevs/juices
92531150	PINEAPPLE-ORANGE-GRAPEFRUIT JUICE DRINK W/VITAMIN C	Carb bevs/juices
92531210	SRAWBERRY-FLAVORED DRINK W/ VITAMIN C ADDED	Carb bevs/juices
92541010	FRUIT-FLAVORED DRINK, FROM SWEETENED PWDR,FORTIFIED W/ VIT C	Carb bevs/juices
92541100	APPLE CIDER DRINK, FROM MIX, SUGAR & VIT C ADDED	Carb bevs/juices
92541120	APPLE CIDER DRINK, FROM MIX, LOW CAL, VIT C ADDED	Carb bevs/juices
92550050	APPLE-WHITE GRAPE JUICE DRINK,LOW CAL,W/VIT C ADDED	Carb bevs/juices
92550110	CRANBERRY JUICE COCKTAIL, LO CAL, W/ VIT C ADDED	Carb bevs/juices

92550210	CRANBERRY-APPLE JUICE DRINK, LO CAL, VIT C ADDED	Carb bevs/juices
92550300	GRAPEFRUIT JUICE DRINK,LOW CALORIE,W/ VITAMIN C	Carb bevs/juices
92550610	FRUIT-FLAVORED DRINK, LOW CAL, W/ VITAMIN C ADDED	Carb bevs/juices
92551600	CITRUS JUICE DRINK, LOW CALORIE	Carb bevs/juices
92551700	JUICE DRINK, LOW CALORIE	Carb bevs/juices
92552000	FRUIT-FLAV DRINK, FROM MIX, HI VIT C ADDED, LOW CAL	Carb bevs/juices
92552050	ORANGE BREAKFAST DRINK, LOW CALORIE	Carb bevs/juices
92552100	ORANGE-CRANBERRY JUICE DRINK,LOW CAL,W/ VIT C ADDED	Carb bevs/juices
92553000	FRUIT-FLAVORED THIRST QUENCHER BEVERAGE, LOW CAL	Carb bevs/juices
92560000	FRUIT-FLAVORED THIRST QUENCHER BEVERAGE	Carb bevs/juices
92570100	FLUID REPLACEMNT,ELECTROLYTE SOLUTN(INCL PEDIALYTE)	Carb bevs/juices
92570500	FLUID REPLACEMENT, 5% GLUCOSE IN WATER	Carb bevs/juices
92582000	FRUIT-FLAVORED DRINK, LOW CALORIE, CALCIUM-FORTIFD	Carb bevs/juices
92582050	FRUIT-FLAVORED DRINK, VITAMIN & MINERAL FORTIFIED	Carb bevs/juices
92582100	CITRUS JUICE DRINK, CALCUIM FORTIFIED	Carb bevs/juices
92582110	ORANGE BREAKFAST DRINK, CALCIUM FORTIFIED	Carb bevs/juices

Appendix D

GRAS Expert Panel Critical Evaluation of Tea Catechin

THE GENERALLY RECOGNIZED AS SAFE STATUS OF GREEN TEA CATECHIN

OPINION OF AN EXPERT PANEL

February 20, 2007

INTRODUCTION

Kao Corporation convened a panel of independent, internationally recognized biomedical scientists ("the Expert Panel"), qualified by their scientific training and experience to evaluate the safety of food and food ingredients, to independently and collectively critically evaluate available published and unpublished information on Green Tea Catechin ("GTC") to determine its safety and generally recognized as safe ("GRAS") status under the proposed conditions of use based on scientific procedures.

The members of the Expert Panel included Professors Joseph F. Borzelleca of the Virginia Commonwealth University, Medical College of Virginia, James W. Anderson, of the University of Kentucky School of Medicine, and Michael W. Pariza of the University of Wisconsin, Madison. The curricula vitae of the panelists are provided in Appendix 1.

Morgan, Lewis & Bockius LLP ("Morgan Lewis") conducted a thorough search of the scientific literature on Green Tea Catechin and related compounds through November 1, 2006. The results of these searches were available to the Expert Panel. Kao Corporation and Morgan Lewis also provided to the panelists a comprehensive package of appropriate information including the methods of manufacture, specifications, batch analyses, proposed uses, exposure estimates, and safety. The Expert Panel independently and collectively critically evaluated these materials and other materials deemed appropriate or necessary and consulted by telephone. The Expert Panel unanimously concluded that Green Tea Catechin, meeting appropriate food grade material specifications, and manufactured and used as described herein and consistent with current Good Manufacturing Practice, is safe and GRAS based on scientific procedures.

A summary of the basis for this GRAS determination follows.

Identity and Characterization

GTC is a mixture of eight catechin monomers that is extracted from crude green tea extract and includes polyphenols, caffeine, organic acids, protein and amino acids, saccharide, fiber, fat, and ash.

Manufacturing, Specifications, Batch Analyses

Green Tea Catechin is manufactured from green tea extract (the primary ingredient), which is mixed with a water/ethanol solution to dissolve the catechin monomers present in the green tea extract. The ethanol/water solution containing the dissolved monomers is filtered by centrifugation, and the catechin monomers are then purified by adsorption to activated carbon. The extract containing the highly-concentrated catechin monomers is dried and the residual ethanol allowed to evaporate. The extract is then sterilized (92° for 2 minutes), inspected and

packaged as a brown aqueous solution. The product formed, GTC, is a water-soluble complex mixture of tea catechins. For the purpose of altering the taste of some beverages, a tannase-treated version of the GTC is sometimes employed in manufacturing process (referred to as "Tannase-treated GTC").

Sensitive chemical and microbiological analyses have failed to identify potential human toxins in GTC.

Batch analyses demonstrate consistency of production. GTC is stable for at least one year as a liquid and/or at least six months in beverages.

All ingredients used in the manufacture of GTC are used in food and beverage manufacturing and are approved by the U.S. FDA.

Regulatory Status

Green tea extract has been granted GRAS status by the U.S. Food and Drug Administration ("FDA") (21 C.F.R. § 182.20). FDA has affirmed clay as GRAS for use as an indirect food substance (21 C.F.R. § 186.1256), and ethanol as GRAS for use as a direct food substance (21 C.F.R. § 184.1293). Tannase is self-GRAS in the U.S. Active carbon and diatomaceous earth are widely used in the beverage manufacturing industry worldwide to refine beverages. Powdered cellulose has served as a food ingredient in the U.S. for nearly 85 years.

Exposure, Proposed Uses, and Estimated Daily Intake (EDI)

GTC is intended for use as a natural extract in beverages, including bottled teas, sports drinks, carbonated soft drinks, and juice. The estimated intake of Green Tea Catechin for the U.S. population was determined from appropriate databases including USDA's 1994-96 and 1998 CSFII surveys and reported in the dossier. These findings are summarized in the context of four scenarios:

Intake Scenario	**mg/kg-bw/day, Mean (90th percentile)**
Scenario 1: Consumers (US Population, 2+ years) of all bottled tea in the U.S. will switch to GTC beverage	4.3 (7.8)
Scenario 2: Consumers US Population, 2+ years) of all bottled of sports drinks in the U.S. will switch to GTC beverage	6.5 (13.5)
Scenario 3: Consumers (US Population, 2+ years) of all bottled of carbonated beverages and juices in the U.S. will switch to GTC beverage	10.2 (21.2)
Scenario 4: Consumers (US Population, 2+ years) of all bottled of combined bottled tea, sports drinks, carbonated beverages, and juices in the U.S. will switch to proposed beverage	10.4 (21.5)

As of June, 2006, Kao has sold 614 million bottles of Green Tea Catechin drinks in Japan.

Self-Limiting Levels of Use

Although no limits on the use of GTC have been established, its bitter, astringent taste likely would limit its use at high levels.

Biological Data Relating to Safety

The safety of GTC has been established by a series of published and unpublished studies, including acute oral (rat), subacute (rat, 14 days and 28 days), and genotoxicity (bacterial reverse mutation assay (Ames test), chromosomal aberration assay in cultured Chinese hamster ovary cells, mouse lymphoma L5178/tk assay, and mouse bone marrow micronucleus test). Due to a heat-sterilization step in the manufacture of one type of Green Tea Beverage, many of these studies were conducted in parallel with both a heat-treated ("HT-GTC") and non-heat-treated version of Green Tea Catechin ("UT-GTC"). Published studies on catechin mixtures similar in composition to GTC (essentially equivalent) demonstrate a lack of toxicity of the constituents of GTC following oral subchronic (rat, 6-month), irritation potential, and reproductive/developmental toxicity (rat). In addition, published studies provide information on the absorption, distribution, metabolism, and excretion, and toxicology of individual catechin or similar catechin mixtures.

Safety data are primarily limited to *in vitro* and animal studies. However numerous studies assessing the efficacy of GTC in humans for fat reduction report useful safety data including hematology, clinical chemistry, and adverse event reporting, and these data support the safety of GTC. The weight of the available evidence demonstrates the safety of GTC for the proposed use.

Absorption, Distribution, Metabolism and Excretion

Green Tea Catechins are poorly absorbed from the gastrointestinal tract (< 10% of the oral dose), distributed in the gastrointestinal mucosa, and excreted in feces via bile. Five to 8% of ingested GTC is absorbed within a relatively short time and partially conjugated with glucuronide and sulfate in microepithelial cells upon absorption.

Acute Oral Toxicity Studies of Green Tea Catechin

The acute oral toxicity of HT-GTC was assessed in male and female Sprague-Dawley rats at a dose of 2000 mg/kg-bw. No deaths or signs of clinical abnormalities were reported.

In an additional study of HT-GTC in male and female albino rats at doses of either 2000 mg/kg-bw or 5000 mg/kg-bw, one male and one female administered 5000 mg/kg-bw died 1 or 2 days after administration. In the 2000 mg/kg-bw group, 2 out of 6 females died 2 or 3 days after administration, and no males died. Based on the above results, the acute oral LD_{50} of HT-GTC was estimated to be greater than 2000 mg/kg-bw

An estimated LD_{50} of 4647.29 mg/kg-bw in mice was reported for Polyphenon 30, a mixture of catechins similar to GTC.

14-Day Oral Toxicity Studies of Green Tea Catechin (HT-GTC and UT-GTC)

GTC was administered to male and female Sprague-Dawley rats for 14 days at doses of 500, 1000, or 2000 mg/kg-bw/day. The No-Observed-Adverse-Event-Level ("NOAEL") for HT-GTC was determined to be 500 mg/kg-bw/day for males based on decreased body weight and body weight gain, and 2000 mg/kg-bw/day for females, the highest dose tested. A NOAEL of 2000 mg/kg-bw/day was observed for UT-GTC.

28-Day Oral Toxicity Studies of Green Tea Catechin (GTC)

GTC (UT-GTC, HT-GTC, or decaffeinated HT-GTC) was administered to male and female Sprague-Dawley rats for 28 days at doses of 500, 1000 or 2000 mg/kg-bw/day.

The NOAEL for HT-GTC was 1000 mg/kg-bw/day based on the lack of *local toxicity* (e.g., gastric erosions). The NOAEL for *systemic toxicity* was 2000 mg/kg-bw/day, the highest dose tested. Study findings for the 2000 mg/kg/day decaffeinated version of HT-GTC animals were similar to the 2000 mg/kg-bw/day HT-GTC-treated animals, with the following exceptions: body weights and body weight gains were similar to the control animals and there were no microscopic findings in any of the tissues examined

The NOAEL for UT-GTC was 2000 mg/kg bw/day (the highest dose tested).

Six-Month Oral Toxicity Study of Polyphenon 70S

A NOAEL of 1000 mg/kg-bw/day was reported for Polyphenon 70S (a mixture of catechins highly similar to GTC) in rats. In the 2000 mg/kg-bw/day group, the weight of the liver increased with concomitant elevations in plasma alkaline phosphatase and GPT and a slight degeneration of hepatocytes.

Genotoxicity

Three *in vitro* tests were performed with either UT-GTC or HT-GTC. Positive responses were observed in both the chromosomal aberration assay (in Chinese hamster lung cells, CHU/IU) and the mouse lymphoma L5178Y/tk assay but none were reported in the Ames test. The bone micronucleus test in ICR CD mice—an *in vivo* test—revealed no evidence of mutagenicity.

The results of these studies were qualitatively (i.e., positive or negative) equivalent for both UT-GTC and HT-GTC. Although positive findings were reported in the *in vitro* assays, the *in vivo* study failed to demonstrate genotoxicity. A published study on Polyphenon E reported negative results for a bacterial mutagenicity assay, but positive results for the Big Blue CII transgenic mutation assay and mouse micronucleus test.

Reproductive/Developmental Toxicity

In a rat developmental toxicity study, a NOAEL of 1000 mg/kg-bw, the highest dose tested, was reported for Polyphenon E.

Irritation and Sensitization

No evidence of irritation of the oral mucosa either immediately after treatment or 24 hours thereafter was reported for Polyphenon E.

Sensitization studies on GTC or related substances were not identified in the literature search.

Studies in Humans

A series of short- and longer-term clinical investigations on substances similar to GTC examining tolerability, safety, and nutritional effects in humans including clinical chemistry, hematology, urinalysis, and self-reported adverse event data demonstrated tolerability and no adverse health effects.

Summary and Discussion

Green Tea Catechin is a mixture of eight catechins extracted from green tea leaves, which also includes polyphenols, caffeine, organic acids, protein and amino acids, saccharide, and ash. GTC is intended for use as a natural extract in beverages, including bottled teas, sports drinks, carbonated soft drinks, and juice. For the purpose of modifying taste in some of these beverages, GTC is sometimes slightly altered by treatment with tannase. The constituents of GTC are poorly absorbed, distributed in the gastrointestinal mucosa, and excreted in feces via bile. There is no evidence that GTC accumulates in the body and elicits toxicity.

A critical evaluation of available information on the safety of GTC in animals and in humans indicates that it is a relatively non-toxic substance at the doses tested.

The upper estimated daily intake (i.e., scenario 4 described above) from all proposed uses is 10.4 mg/kg bw/day at the mean and 21.5 mg/kg bw/day at the 90th percentile.

Conclusion

Based on its independent and collective critical evaluation of the data and information currently available on GTC, the Panel concludes that GTC manufactured and used as described herein (consistent with current Good Manufacturing Practice), and meeting appropriate specifications for food grade material, is safe for the intended uses described herein.

The Panel also concludes that other experts qualified by scientific training and experience, and evaluating the same data and information, would generally recognize that GTC is safe for the uses described herein.

The Panel further concludes GTC is GRAS based on scientific procedures for the uses described herein. This is supported by a relatively long history of safe use of green tea and its extracts.

23 February 2007

Joseph F. Borzelleca, Ph.D., Chair
Professor Emeritus, Pharmacology & Toxicology
Virginia Commonwealth University
Medical College of Virginia

15 March 2007

James W. Anderson, ~~Ph.D.~~ M.D.
Professor Medicine and Clinical Nutrition;
Director, HMR Weight Management Program
Endocrine Division
University of Kentucky School of Medicine

10 March 2007

Michael W. Pariza, Ph.D.
Wisconsin Distinguished Professor of Food Microbiology and Toxicology
Director, Food Research Institute
University of Wisconsin, Madison

Appendix E

Curricula Vitae of Expert Panel Members

Curriculum Vitae

Joseph F. Borzelleca, Ph.D.

Personal History

Name.
Address·

S.S. No: upon request
Citizenship· United States

Telephone:

Fax.

Email·

University Address
Dept. of Pharmacology and Toxicology
Medical College of Virginia
Virginia Commonwealth University
Box 980613
Richmond, VA 23298-0613

Educational Background

B.S.	St. Joseph's University, Philadelphia, PA Biology, Chemistry	1952
M S.	School of Graduate Studies Thomas Jefferson University Jefferson Medical College, Philadelphia, PA Pharmacology, Physiology	1954
Ph.D	School of Graduate Studies Thomas Jefferson University Jefferson Medical College, Philadelphia, PA Pharmacology, Biochemistry	1956

Academic Appointments

Department of Pharmacology Medical College of Pennsylvania Philadelphia, PA	Instructor-Associate	1956-1959
Department of Pharmacology and Toxicology Medical College of Virginia Richmond, VA 23298-0613	Assistant Professor	1959-1962
	Associate Professor	1962-1967
	Professor	1967-
	Head, Division of Toxicology	1972-1986
	Professor Emeritus	01 July 1996-

Professional Certification

Fellow, Academy of Toxicological Sciences

Professional Affiliations

Societies

Academy of Toxicological Sciences* **
American Association for the Advancement of Science
American Chemical Society
American College of Toxicology*
American Society of Pharmacology and Experimental Therapeutics**
(Environmental Pharmacology Committee; Liaison Committee, SOT; Toxicology Committee)
Institute of Food Technologists (Professional Member)
International Society of Regulatory Toxicology and Pharmacology*
(Member of Council)
Sigma Xi
Society of Experimental Biology and Medicine*
(Councilor; Program Chairman of Southeastern Section)
Society of Toxicology* **
(Member and/or Chairman: Awards, Education, Legislative Affairs, Membership, Nominating Committees; Secretary of the Society, Councilor, and President; President, Food Safety Specialty Section)
Virginia Academy of Science*
(Chairman, Medical Sciences Division)

* Held elected office
** Held appointed office or position

Board of Directors

ILSI (until 2002)

Board of Scientific and Policy Advisors

American Council on Science and Health (until 2000)

Journals

Editor, Food Chemical Toxicology, 1992-

Editorial Board
Environmental Carcinogenesis Reviews, 1981-2000
Journal of Environmental Pathology,Toxicology and Oncology 1977- 2000
Journal of Environmental Science and Health, 1979-2004
Journal of the American College of Toxicology, 1982-
Journal of Toxicology: Cutaneous and Ocular Toxicology, 1982- 1992
Journal of Applied Toxicology, 1989-
Pharmacology, 1978-
Pharmacology and Drug Development, 1980-
Toxicology and Applied Pharmacology, 1975-1978

Consultantships (Past, Present)

Governmental

Food and Drug Administration
National Institute of Mental Health
National Cancer Institute
Environmental Protection Agency
Department of Labor - OSHA (Chairman, Carcinogens Standards Committee)
U.S. Army - Research and Development Command

Non-Governmental

National Academy of Sciences - NRC
Committee on Toxicology (Member, Chairman)/Board on Toxicology and Environmental Health Hazards
Safe Drinking Water Committee
Evaluation of Household Substances Committee (1138 Committee)
Food Protection Committee
Food Additives Survey Committee
Committee on Risk-Based Criteria for Non-RCRA Hazardous Wastes
Committee on Risk Assessment of Flame-Retardant Chemicals
Food Chemicals Codex Committee

Federation of American Societies of Experimental Biology
Select Committee on GRAS Substances
Flavors and Extracts
Biotechnology Product Safety
Caprenin GRAS Committee

World Health Organization
Joint Meeting on Pesticide Residues (JMPR) (Member, Chairman)

NATO/CCMS Drinking Water Committee

Industrial

Chemical Companies, Trade Associations

University Activities

Related to Instruction

Prepared a laboratory manual in pharmacology (animal and human studies) (1960)
Introduced the use of closed circuit TV and TV tapes in pharmacology (1960)
Introduced clinical pharmacological experiments into the medical and dental programs (1960)
Planning and participation in continuing education program (Schools of Dentistry, Medicine and Pharmacy)
Planning and administration: each of the three major efforts in pharmacology (dental, medical, pharmacy)
Graduate Program - assisted in developing graduate training program in toxicology

Current Teaching Activities

Present lectures on Toxicological Issues, Food Intake and Control

Not Directly Related to Instruction

Elected senator from the graduate school, then vice-president of the University Senate
Served on various committees (e.g. Curriculum, Search, Animal Care,) in each of the four major schools (Dentistry, Graduate, Medical, Pharmacy)

Research

Research was continuously funded from 1956. Sources of support included governmental (U.S.P.H.S.; N.I.H; E.P.A.; N.I.D.A.) and non-governmental (industrial) (A list of publications is attached).

Awards

DOD - US Army - Chemical Research Development and Engineering Center
Distinguished Service Award, 1986

National Italian - American Foundation Award
Excellence in Medicine and Community Service, 1987

Thomas Jefferson University
Distinguished Alumnus Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences
Outstanding Faculty Award, 1987

Virginia Commonwealth University, Dept. of Pharmacology and Toxicology
Professor of the Year- 1992

American College of Toxicology
Distinguished Service Award - 1997

Virginia's Life Achievement in Science Award- April 2001

Bernard L. Oser Food Ingredient Safety Award by the Institute of Food Technologists- June 2001

International Society for Regulatory Toxicology and Pharmacology's International Achievement Award for 2001- December 2001

Society of Toxicology - Education Award- March 2002

PUBLICATIONS

Borzelleca, J.F. and Manthei, R.W.: Factors influencing pentobarbital sleeping time in mice. Arch. Int. Pharmacodyn. Ther. 111: 296, 1957.

Borzelleca, J.F.: Studies of the contribution of bladder absorption to the physiological changes induced by pentobarbital. J. Pharm. Exp. Ther. 129: 305, 1960.

Borzelleca, J.F.: The absorption of nicotine from the urinary bladder of the dog. Arch. Int. Pharmacodyn. Ther. 133: 444, 1961.

Borzelleca, J.F , Bowman, E.R. and McKennis, H., Jr . The cardiovascular and respiratory effects of (-)-cotinine. J. Pharmacol. Exp. Ther 137 313, 1962.

Borzelleca, J.F.: Drug absorption from the urinary tract of the rat. Nicotine. Arch. Int Pharmacodyn. Ther. 143: 595, 1963.

Borzelleca, J.F.: Influence of saline and glucose infusions on the course of barbiturate intoxication. Arch. Int. Pharmacodyn. Ther. 146: 163, 1963.

Larson, P.S , Borzelleca, J.F., Bowman, E.R., Crawford, E.M., Smith, R.B., Jr. and Henningar, G.R.: Toxicologic studies on a preparation of p-tertiary octylphenoxy-polyethoxy ethanols (Trition X-405). Toxicol Appl. Pharmacol. 5: 782, 1963.

Borzelleca, J.F., Larson, P.S., Henningar, G.R., Hug, E.G., Crawford, E.M. and Smith, R.B., Jr.. Studies on the chronic oral toxicity of monomeric ethyl acrylate and methyl methacrylate. Toxicol. Appl. Pharmacol. 6: 29, 1964.

Borzelleca, J.F. and Cherrick, H.: The excretion of drugs in saliva. Antibiotics J. Oral Ther. Pharmacol. 2: 180, 1965.

Borzelleca, J.F. and Lester, D.. Acute toxicity of some perhalogenated acetones. Toxicol. Appl. Pharmacol. 7: 592, 1965.

Borzelleca, J.F.: Drug movement from the isolated urinary bladder of the rabbit. Arch. Int. Pharmacodyn Ther. 154: 40, 1965.

Borzelleca, J.F.: Rabbit urinary bladder potentials. Invest. Urology 3: 77, 1965.

Borzelleca, J.F.: Studies on the mechanisms of drug movement from the isolated urinary bladder. J. Pharmacol. Exp. Ther. 148: 111, 1965.

Lowenthal, W. and Borzelleca, J.F.: Drug absorption from the rectum. I. J Pharm. Sci. 54. 1790, 1965.

Ambrose, A.M., Borzelleca, J.F., Larson, P.S., Smith, R.B., Jr and Henngar, G.R.: Toxicologic studies on monochloroacetaldehyde: 2,4-dinitrophenylhydrazone, a foliar fungicide. Toxicol. Appl. Pharmacol. 8: 472, 1966.

Borzelleca, J F. and Doyle, C.H.: Excretion of drugs in saliva. Salicylate, barbiturate, sulfanilamide. J Oral. Ther. Pharmacol. 3: 104, 1966.

Borzelleca, J.F and Lowenthal, W.: Drug absorption from the rectum. II. J Pharm Sci. 55: 151, 1966

Wooles, W.R and Borzelleca, J F.: Prolongation of barbiturate sleeping time in mice by stimulation of the reticuloendothelial system. J Reticuloendothel Soc 3 41, 1966.

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Wooles, W.R., Borzelleca, J.F. and Branham, G.W.: The effects of acute and prolonged salicylate administration on liver and plasma triglyceride levels and dietary-induced hypercholesterolemia. Toxicol. Appl. Pharmacol. 10: 1, 1967

Borzelleca, J.F., Harris, T. and Bernstein, S.: The effect of DMSO on drug movement through the wall of the urinary bladder of the rabbit. J. Invest. Urol. 6: 43, 1968

Borzelleca, J.F.: The excretion of glucose in saliva Dog. J. Oral Ther. Pharmacol. 4: 338, 1968.

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Borzelleca, J F. and Putney, J.W., Jr.: A model for the movement of salicylate across the parotid epithelium. J. Pharmacol. Exp. Ther. 174: 527, 1970.

Borzelleca, J.F. and Putney, J.W., Jr. Studies on the biotransformation of salicylic acid by the salivary gland. Arch. Int. Pharmacodyn. Ther. 188: 127, 1970.

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Putney, J.W., Jr. and Borzelleca, J.F.: A method for the determination of small quantities of salicylate metabolites in the presence of a great excess of salicylic acid. Arch. Int. Pharmacodyn. Ther. 188: 119, 1970.

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Putney, J.W., Jr. and Borzelleca, J F.: On the mechanisms of ^{14}C-nicotine distribution in rat submaxillary gland in vitro. J. Pharmacol. Exp Ther. 178: 180, 1971.

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Updated 2/9/06

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Adams, M.D., Wedig, J.H , Jordan, R.L., Smith, L.W., Henderson, R. and Borzelleca, J.F.: Urinary excretion and metabolism of salts of 2-pyridinethiol-1-oxide following intravenous administration to female yorkshire pigs. Toxicol. Appl. Pharmacol. 36: 523, 1976.

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Evaluation of the health aspects of calcium pantothenate, sodium pantothenate, and D-pantothenyl acohol as food ingredients. 1978

Evaluation of the health aspects of Vitamin B12 as a food ingredient. 1978.

Evaluation of the health aspects of Vitamin D2 and Vitamin D3 as food ingredients. 1978.

Evaluation of the health aspects of caffeine as a food ingredient. 1978.

Evaluation of the health aspects of certain glutamates as food ingredients. 1978.

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1978

Evaluation of the health aspects of butylated hydroxyanisole as a food

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB):

ingredient. 1978.

Evaluation of the health aspects of sodium, potassium, magnesium and zinc gluconates as food ingredients 1978.

Evaluation of the health aspects of urea as a food ingredient. 1978.

Evaluation of the health aspects of thiamin hydrochloride and thiamin mononitrate as food ingredients 1978.

Evaluation of the health aspects of biotin as a food ingredient. 1978.

Evaluation of the health aspects of ascorbic acid, sodium ascorbate, calcium ascorbate, erythorbic acid, sodium erythorbate, and ascorbyl palmitate as food ingredients. 1979.

Evaluation of the health aspects of propionic acid, calcium propionate, sodium propionate, dilauryl thiodipropionate, and thiodipropionic acid as food ingredients. 1979.

Evaluation of the health aspects of casein, sodium caseinate, and calcium caseinate as food ingredients. 1979.

Evaluation of the health aspects of nickel as a food ingredient. 1979

Evaluation of the health aspects of soy protein isolates as food ingredients. 1979.

Evaluation of the health aspects of carotene (B-carotene) as a food ingredient. 1979.

Evaluation of the health aspects of nitrogen, helium, propane, n-butane, isobutane, and nitrous oxide as gases used in foods. 1979.

Evaluation of the health aspects of hydrogen peroxide as a food ingredient. 1979.

Evaluation of the health aspects of riboflavin and riboflavin-5-1-phosphate as food ingredients. 1979.

Evaluation of the health aspects of starch and modified starches as food ingredients. 1979.

Evaluation of the health aspects of carbon dioxide as a food ingredient. 1979.

Evaluation of the health aspects of sodium chloride and potassium chloride as food ingredients. 1979.

Evaluation of the health aspects of certain silicates as food ingredients. 1979.

Evaluation of the health aspects of manganous salts as food ingredients 1979.

Evaluation of the health aspects of copper gluconate, copper sulfate, and cuprous iodide as food ingredients 1979.

Evaluation of the health aspects of hydrochloric acid as a food ingredient. 1979

Evaluation of the health aspects of lecithin as a food ingredient. 1979

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB):

Evaluation of the health aspects of potassium acid tartrate, sodium potassium tartrate, sodium tartrate and tartaric acid as food ingredients. 1979.

Evaluation of the health aspects of starter distillate and diacetyl as food ingredients. 1980.

Vitamin A, Vitamin A Acetate, and Vitamin A Palmitate as food ingredients 1980.

Evaluation of the health aspects of iron and iron salts as food ingredients. 1980

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1980.

Evaluation of the health aspects of collagen as a food ingredient. 1981.

Evaluation of the health aspects of methyl polysilicones as food ingredients. 1981.

Evaluation of the health aspects of soya fatty acid amines as food ingredients. 1981.

Evaluation of the health aspects of activated carbon (charcoal) as a food processing aid. 1981.

Evaluation of the health aspects of smoke flavoring solutions and smoked yeast flavoring as food ingredients. 1981.

Evaluation of the health aspects of commint oil as a food ingredient. 1981.

Evaluation of the health aspects of a mixture. Evaluation of the health aspects of diferrous, dipotassium ferrous, and potassium ferrocyanides as finding agents in wine production. 1981.

Evaluation of the health aspects of wheat gluten, corn gluten, and zein as food ingredients. 1981.

Evaluation of the health aspects of peptones as food ingredients. 1981

Evaluation of the health aspects of shellac and shellac wax as food ingredients. 1981.

Evaluation of the health aspects of sodium metasilicate and sodium zinc metasilicate as food ingredients. 1981.

Evaluation of the health aspects of oat gum, okra gum, quince seed gum, and psyllium seed husk gum as food ingredients. 1982.

Contributing Authorship on the Following Publications of the National Academy of Sciences:

Principles and Procedures for Evaluating the Toxicity of Household Substances
Committee for the Revision of NAS Publication 1138, Committee on Toxicology, Assembly of Life Sciences, National Research Council, National Academy of Sciences
National Academy Press, Washington, D.C. 1977

Drinking Water and Health.
Safe Drinking Water Committee, Board on Toxicology and Environmental Health Hazards, Assembly of Life Sciences, National Research Council, National Academy of Sciences
Volume 1, 1977, Volume 2, 1980, Volume 3, 1980
National Academy Press, Washington, D.C.

Estimating Consumer Exposure to Food Additives and Monitoring Trends in Use.
Food Additives Survey Committee, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. National Academy Press, Washington, D.C 1992

Examination of Dietary Recommendations for Salt-Cured, Smoked, and Nitrite-Preserved Foods.
Pariza, M.W., Borzelleca, J.F , Cassens, R.G., Filer, L.J., and Kritchevsky, D.,
CAST Issue Paper Number 8, November 1997

Updated 2/9/06

Curricula Vitae for James W. Anderson

Andersonlab News Articles Calendar Bio Contact

James W. Anderson

Metabolic Research Group

General

Professional

Committees

Education	1965	M.S. Mayo Graduate School
	1961	M.D. Northwestern University
	1958	B.A. W. Virginia University
Training	1962-65	Fellow in Medicine and Endocrinology Mayo Clinic, Rochester, Minnesota
	1961-62	Internship, Presbyterian Hospital, Denver, Colorado
Faculty Appointments	1985-Present	Medical Director HMR Fasting Program University of Kentucky
	1983-84	Visiting Scientist Massachusetts Institute of Technology Cambridge Massachusetts
	1980-83	Chief, Medical Service VA Medical Center, Lexington, KY
	1978-Present	Professor of Medicine University of Kentucky College of Medicine Professor of Clinical Nutrition Lexington, Kentucky
	1973-78	Associate Professor of Medicine University of Kentucky College of Medicine
	1973	Chief, Endocrine-Metabolic Section VA Medical Center, Lexington, Kentucky
	1968-73	Assistant Professor of Medicine University of California Medical School, San Francisco, California
Certifications	1975	American Board Internal Medicine
	1973	Kentucky
Military	1965-68	U.S. Army, Denver, CO (Captain) Chief, Metabolic-Renal Section

Research Endocrinologist, Nutrition
Research Laboratory Fitzsimons
Hospital

Andersonbig News Articles Calendar Bio Contact

General

Professional Committees

Professional Organizations	Alpha Omega Alpha American College of Nutrition - Fellow American College of Physicians - Fellow American Diabetes Association American Federation for Clinical Research American society for Clinical Nutrition Endocrine Society Society for Experimental Biology and Medicine	
Editorial Board	1974-77	American Journal of Clinical Nutrition
	1987-89	Diabetes: Self-Management Prevention Magazine
	1990-96	Diabetes in the News
	1991-97	Medicine, Exercise, Nutrition and Health
	1997	Vegetarian Nutrition
	1998	PRIME Health & Fitness
Reviewer	American Journal of Clinical Nutrition American Journal of Medicine Annals of Internal Medicine Archives of Internal Medicine Diabetes Diabetes Care Diabetolgia Journal of the American Medical Association Journal of Laboratory and Clinical Medicine Journal of Nutrition Journal of American College of Nutrition Journal of American Dietetic Association Journal of Clinical Endocrinology and Metabolism Metabolism New England Journal of Medicine	
Editor	1979-	HCF Diabetes and Nutrition Newsletter (Circulation 10,000)
Professional Services	1997	American College of Nutrition Board of Directors
	1994	1974-77Special Study Section: NIDDK for "NIDDM" Primary Prevention Trial
	1988-	Diabetes Advisory Committee Kentucky Diabetes control Program
	1986	LSRO-FDA Expert Panel on Dietary Fiber

000120

1985-86	NIH Diabetes and Hypertension Treatment Panel
1982-86	Scientific Advisory Committee - Wheat Industry
1975-76	Kentucky Diabetes Association President

News Articles Calendar Bio Contact

Committees	1996-	Executive Commitee-Nutrition Graduate Program
	1994-95	Medical Center Clinical Sciences Area, Advisory
	1991-93	University of Kentucky/Veterans Affairs Research Advisory Committee
	1990-93	University of Kentucky Press Committee, Nutrition Focus Committee
	1989-	Nutrition Focus Committee, Department of Nutrition and Food Science
	1987	Coordinated Program Advisory Committee, Department of Nutrition and Food Science
	1979-82	Faculty, Promotions and Tenure Committee
VAMC Committees	1993	SDTU Ad-Hoc Committee, Chairman
	1986	Pharmacy Committee
	19781-83	Medical Intensive Care Committee, Chairman
	1981-83	Ambulatory Care Committee, Chairman
	1980-83	Clinical Executive Board
University Hospital Department of Medicine	1993-	Nutrition Committee
	1992	Problem Based Learning Committee
	1988-90	Board of Directors, Association for Medical Research
	1986-96	Faculty Promotions Committee
	1980-88	Chairman's Advisory Committee

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Curricula Vitae for Michael W. Pariza

MICHAEL W. PARIZA - CURRICULUM VITAE

Academic Rank: Director, Food Research Institute; Wisconsin Distinguished Professor and Chair, Department of Food Microbiology and Toxicology.

Education:

Ph.D.	Kansas State University	1973	Microbiology
M.Sc.	Kansas State University	1969	Microbiology
B.Sc.	University of Wisconsin-Madison	1967	Bacteriology

Professional Experience:

- Kansas State University: Graduate Teaching Assistant, Graduate Research Assistant, 1967-1969.
- U.S. Army (Armed Forces Institute of Pathology, Washington, D.C.): Biological Sciences Assistant, 1969-1971.
- Kansas State University: Graduate Teaching Assistant, Graduate Research Assistant, 1971-1973.
- The University of Wisconsin-Madison (McArdle Laboratory for Cancer Research): NIH Postdoctoral Traineeship with Professor Van R. Potter, 1973-1976.
- The University of Wisconsin-Madison (The Food Research Institute, Department of Food Microbiology and Toxicology): Assistant Professor, 1976-1981; Associate Professor, 1981-1984; Professor, 1984-Present; Associate Department Chair, 1981-1982; Department Chair, 1982-Present; Director, Food Research Institute, 1986-present.
- Wisconsin Distinguished Professor, 1993-present.
- Affiliate appointments at the University of Wisconsin: Wisconsin Comprehensive Cancer Center; Environmental Toxicology Center; Department of Nutritional Sciences; Department of Food Science.

Membership in Scientific Organizations:

The American Association for Cancer Research
The American Society for Microbiology
The American Association for the Advancement of Science
The Society of Sigma Xi
The Institute of Food Technologists
The Toxicology Forum
FASEB (The American Institute of Nutrition; The American Society for Clinical Nutrition)
The American Chemical Society
The American Oil Chemists' Society

Special Professional Recognition (1986-present):

- Co-Chair of Organizing Committee, Co-Editor of Proceedings, and Keynote Speaker for an international symposium entitled "Calories and Energy Expenditure in Carcinogenesis," held in Washington, DC, in 1986.
- Chair, Food Microbiology Division of the American Society for Microbiology, 1986/87.

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Appendix F

Japan Ministry of Health, Labor and Welfare, *Permit for Labeling a Product as a Food for Specified Health Use* (green tea and oolong tea)

Health, Labor and Welfare

Ministry Food Product Evaluation No. 306001

Permit for labeling a product

as a Food for Specified Health Use

Name of applicant: Kao Corporation

With respect to "Healthya Green Tea" for which application was made on April 18, 2001, I give the applicant permission to indicate "Food for Specified Health Use" on the label of the product concerned as described below, according to Article 12, Paragraph 1 of the Nutrition Improvement Law (Law No. 248 that was enacted in 1952).

March 6, 2003

Chikara Sakaguchi

Minister of Health, Labor and Welfare

[Stamped with the Minister's seal]

Details

Permit number: No. 466

Content of labeling: As this green tea contains a large amount of tea catechin, it is suitable for people who are concerned about body fat.

Others:

As for the "amount of daily intake", the following labeling shall be made.

"Please drink this tea with one bottle per day as a rough standard."

As for the "precautions to take in its intake", the following labeling shall be made.

" • The intake of a large amount of this tea neither cures disease nor promotes health.

• One bottle of this tea contains 80 mg of caffeine, so please observe the recommended daily intake."

If any new fact concerning the health care effect or safety of this food product is found, it shall be promptly reported to the Office of Health Policy on Newly Developed Food in the Policy Planning Division of Dept. of Food Safety, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor and Welfare.

厚生労働省発食第0306001号

特定保健用食品表示許可書

申請者　花王株式会社

平成１３年４月１８日付で申請のあった「ヘルシア緑茶」について、栄養改善法（昭和２７年法律第２４８号）第１２条第１項の規定により、下記のとおり特定保健用食品の表示をすることを許可する。

平成１５年３月６日

厚生労働大臣　坂口　力

記

許可番号　第４６６号

表示内容　この緑茶は茶カテキンを豊富に含んでいるので、体脂肪が気になる方に適しています。

その他

一日当たりの摂取目安量として、次のような表示を行うこと。

『１本を目安にお飲みください。』

摂取をする上での注意事項として、次のような表示を行うこと。

『・多量摂取により疾病が治癒したり、より健康が増進するものではありません。
・本品は１本当たりカフェインを８０ｍｇ含有します。１日当たりの摂取目安量をお守りください。』

なお、当該食品の保健の効果又は安全性につき、新たな知見を入手した際には、遅滞なく厚生労働省医薬局食品保健部企画課新開発食品保健対策室まで報告すること。

Health, Labor and Welfare

Ministry's Food Product Evaluation No. 306002

Permit for labeling a product

as a Food for Specified Health Use

Name of applicant: Kao Corporation

Withrespectto"HealthyaOolongTea"forwhichapplication was made on April 18, 2001, I give the applicant permission to indicate "Food for Specified Health Use" on the label of the product concerned as described below, according to Article 12, Paragraph 1 of the Nutrition Improvement Law (Law No. 248 that was enacted in 1952).

Chikara Sakaguchi

Minister of Health, Labor and Welfare

[Stamped with the Minister's seal]

Details

Permit number: No. 467

Content of labeling: As this oolong tea contains a large amount of tea catechin, it is suitable for people who are concerned

about body fat.

Others:

As for the "amount of daily intake", the following labeling must be made.

"Please drink this tea with one bottle per day as a rough standard."

As for the "Precautions to take in its intake", the following labeling must be made.

" • The intake of a large amount of this tea neither cures disease nor promotes health.

• One bottle of this product contains 80 mg of caffeine, so please observe the recommended daily intake."

If any new fact concerning the health care effect or safety of this food product is found, it must be promptly informed to the Office of Health Policy on Newly Developed Food in the Policy Planning Division of Dept. of Food Safety, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor and Welfare.

厚生労働省発食第0306002号

特定保健用食品表示許可書

申請者　花王株式会社

平成１３年４月１８日付で申請のあった「ヘルシア烏龍茶」について、栄養改善法（昭和２７年法律第２４８号）第１２条第１項の規定により、下記のとおり特定保健用食品の表示をすることを許可する。

平成１５年３月６日

厚生労働大臣　坂口　力

記

許可番号　第４６７号

表示内容　この烏龍茶は茶カテキンを豊富に含んでいるので、体脂肪が気になる方に適しています。

その他

一日当たりの摂取目安量として、次のような表示を行うこと。

『１本を目安にお飲みください。』

摂取をする上での注意事項として、次のような表示を行うこと。

『・多量摂取により疾病が治癒したり、より健康が増進するものではありません。
・本品は１本当たりカフェインを８０ｍｇ含有します。１日当たりの摂取目安量をお守りください。』

なお、当該食品の保健の効果又は安全性につき、新たな知見を入手した際には、遅滞なく厚生労働省医薬局食品保健部企画課新開発食品保健対策室まで報告すること。

Health, Labor and Welfare

Ministry Food Product Evaluation No. 1209004

Permit for labeling a product

as a Food for Specified Health Use

Name of applicant: Kao Corporation

With respect to "Healthya Water" for which application was made on December 22, 2004, I give the applicant permission to indicate "Food for Specified Health Use" on the label of the product concerned as described below, pursuant to Article 26, Paragraph 1 of the Health Promotion Law (Law No. 103 that was enacted in 2002).

December 9, 2005

Jiro Kawasaki

Minister of Health, Labor and Welfare

[Stamped with the Minister's seal]

Details

Permit number: No. 713

Content of labeling:

As this product contains a large amount of tea catechin and can facilitate the utilization of fat as energy, it is suitable for people who are concerned about body fat.

Others:

As for the rough standard amount of daily intake, the following labeling shall be made.

"Please drink one bottle per day as a rough standard"

As for the precautions to take in its intake, the following labeling shall be made.

" • The intake of a large amount of this drink neither cures disease nor promotes health.

• Excessive intake of this drink may lead to diarrhea depending on your physical constitution or current condition."

For the purpose of popularizing and encouraging a balanced diet, the following labeling shall be made.

"Take a balanced diet based on a combination of staple food, main dishes and side dishes."

If any new fact concerning the health care effect or safety of this food product is found, it shall be promptly reported to the Office of Health Policy on Newly Developed Foods in the Standards and Evaluation Division of the Food Safety, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor and Welfare.

Appendix G

Safety Information on Tannase

Pages 000136 - 000141 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

Supplemental information

"Safety information of Tannase"

Prepared for: Morgan Lewis & Bockius, LLP

1111 Pennsylvania Ave., N.W.

Washington, D.C. 20004

Prepared by : Kao Corporation

Health Care Products Research Labs. No.1

2-1-3 Bunka Sumida-ku

TOKYO 131-8501 JAPAN,

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I. Identity and Regulatory Status

Tannase is an acylhydrolase enzyme preparation from Aspergillus oryzae that can be used as a processing aid for manufacture of cold water-soluble tea beverages.

A. Enzyme Commission number

Tannase is Tannin acylhydrolase, **EC 3.1.1.20**

(http://www.chem.qmul.ac.uk/iubmb/enzyme/index.html)

Common name: tannase

Reaction: digallate + H_2O = **2** gallate

Other name(s): tannase S; tannin acetylhydrolase

Systematic name: tannin acylhydrolase

Comments: Also hydrolyses ester links in other tannins.

Links to other databases: BRENDA, EXPASY, KEGG, ERGO, CAS registry number: 9025-71-2

References: 1. Dyckerhoff, H. and Armbruster, R. Zur Kenntnis der Tannase. *Hoppe- Seyler's Z. Physiol Chem.* 219 (1933) 38-56.

B. CODEX

Tannase is listed in **CODEX** Inventory of Processing Aids

/download/standards/11/CXA_003e.pdf

C. U.S. and Japan

-Tannase is approved for the **food additives in Japan**. (Food additive No.263)

-Self-GRAS in the U.S. (Lipton/ Unilever)

*This information obtained from Tannase manufacturer (Kikkoman).

The published pivotal study to support self-GRAS is ; R.W.LANE, Safety Evaluation of Tannase Enzyme Preparation Derived from Aspergillus oryzae, *Food and Chemical Toxicology*, Vol35, P 207-212 (1997) [1]

D. Other information

Tannase (manufactured by Kikkoman) is approved for the **Kosher** by Union of Orthodox Jewish Congregation of America.

II. Prior Use of Tannase and *Aspergillus oryzae*

A. Prior Use of Tannase

Tannase was originally used in Japan to produce commercial quantities of gallic acid from tannic acid. Tannase has also been used to remove gallic acid from the polyphenols in tea, resulting in beverage that is cold-water-soluble. Tannase is widely used in the U.S. and other countries.

Followings are Tannase manufacturers:

- **Wako Laboratory Chemicals (US, Japan)** http://www wakousa.com/bioproducts/index.html
- **Kikkoman (US, Japan)** http://www kikkoman-usa com/
- **Julich Fine Chemicals (Germany)** http://www.juelich-chemicals de/public/default cfm
- **Great Western Chemical Co. (US)**
  http://www dashinet.com/chemicals/Ads/greatwestern/greatwestern html
- **Enzyme Development Corporation (US)** http://www enzymedevelopment com/
- **SANKYO LIFETECH CO.,LTD. (Japan)** http://www sankyotokuhin net/fdi/syokuhin/list html

Kao is considering the introduction of Tannase manufactured by Kikkoman. Kikkoman has sold Tannase in U.S. for 10 years. (Several tens of metric tons of Tannase per year)

B. Prior Use of *Aspergillus oryzae* [1]

- *Aspergillus oryzae* is a fungus that has been used extensively in producing foods in Japan and the Far East **for perhaps 2000 years.**
- *A. oryzae* is used to make α-amylase for flours in the U.S. (21CFR137.105, 21CFR137.200)
- *A. oryzae* is used to make enzymes for baking and brewing in Europe.
- It is not considered a hazardous micro-organism **(NIH, 1986)**
- Barbesgaard et al. determined that *A oryzae* is not pathogenic or toxigenic to humans.
- The particular strain of A. oryzae used to produce tannase is morphologically equivalent to other strains and is genetically stable
- Tannase strain (Kikkoman Corporation) was originally obtained from a Japanese Koji manufacturer in 1944 (Sakaguchi and Yamada, 1944).

Exemption (b)(4)

IV. Toxicology study (pivotal study to support self-GRAS) [1)]

A 91-day oral toxicity study in the rat and gene mutation study in Salmonella typhimurium were performed to establish the safety of the enzyme preparation for the consumer. General toxicity was low, with no adverse effects observed at highest dose tested, 1 % in the diet.

Table 1. Daily intake of Tannase in subchronic feeding study

Sex	Concn of tannase in diet (%)	Total food consumption (mean, g)	Total tannase consumption (mean, mg)	Body weight (mean for study, g)	Daily tannase dose (mg/kg/day)	Daily tannase Dose (units/kg/day)
M	0	1324	0	232	0	
	0 01	1277	128	228	6.2	
	0 1	1311	1310	231	62 3	
	1 0	1280	12,800	226	622	**31,546** ↓ **(1,577,330units/day) =>50kg body weight**
F	0	939	0	146	0	
	0 01	921	92	145	7.0	
	0.1	951	951	146	71.6	
	1.0	933	9330	146	702	35,604

* In Kao's Green Tea Catechin manufacturing process, residual Tannase will be probably removed during extraction process. On the assumption that Tannase is not removed accidentally, we estimated that residual Tannase is; **20 units/ 1 bottle**

(calculation by used amount of tannase, 1 bottle: sports drink type 500ml)

There is no evidence of mutagenic potential with or without metabolic activation. These results, together with knowledge of the production organism and the chemical and microbiological characterization of the enzyme preparation, indicate that Tannase can be regarded as safe for its intended use in processing tea.

V. Typical Product Characteristics

Tannase treatment remove gallic acid from gallate type Catechins(mainly EGCG).

In current process, weight % of EGCG decreased from 26% to 19 8% and weight % of gallic acid increased from 0.34% to 2.73% (Fig.3). This gallic acid level is almost same level of Pu-erh Tea (Chinese Tea, Table 2)

Table 2. Gallic acid content of tea products

Reference	Gallic acid of green tea	Gallic acid of black tea	Gallic acid of Pu-erh Tea
J. Agric. Food Chem., Vol. 46, No. 9, 1998 [2)]	0.23 % (0.1 %-1.23 %)	1.83 %	1.49 % (0.78 %-2.50 %)
"Kocha-no-Jiten" [3)]	-----	1 %	3 %

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VI. List of References

1. R W. LANE, Safety Evaluation of Tannase Enzyme Preparation Derived from Aspergillus oryzae, *Food and Chemical Toxicology*, Vol35, P 207-212 (1997)
2. Jen-Kun Lin, Survey of Catechins, Gallic Acid, and Methylxanthines in Green, Oolong, Pu-erh, and Black Teas, *J. Agric Food Chem* , Vol 46, No.9, 3635-3642 (1998)
3. Y. Araki and M. Matsuda, *"Kocha-no-Jiten"*, P197 (2002) (Japanese)

Appendix H

Representative Batch Analysis Data for Three Lots of GTC

Representative Lots (GTC)

Analysis data for 3 lots of GTC (Lots: 0404131T, Lots: 0406291T, Lots: 0406031K)

Catechins and Polyphenol	GTC (Lots :0404131T)	GTC (Lots :0406291T)	GTC (Lots :0406031K)
Total Catechin Monomers	42%	39%	43%
Polyphenols	50%	48%	50%
Other components			
Caffeine	3 8%	3.5%	2 3%
Organic acids	7 1%	7.4%	7 6%
Protein and Amino Acids	5 9%	5.6%	5 9%
Saccharide	9.5%	9 6%	9.7%
Fiber	< 0 1%	< 0.1%	< 0.1 %
Fat	< 0.1%	< 0.1 %	< 0 1 %
Ash	2 4%	3.0%	2 3%
Catechin Profile			
Gallocatechin (GC)	3.0%	2.9%	3.3%
Epigallocatechin (EGC)	12.6%	11.4%	12 9%
Catechin (C)	0.9%	0.9%	1.2%
Epicatechin (EC)	3 7%	3.1%	3.3%
Epicatechin gallate (ECG)	5.1%	4.3%	4.6%
Epigallocatechin gallate (EGCG)	16 4%	15.4%	16.1%
Gallocatechin gallate (GCG)	0.8%	0.9%	0 9%
Catechin gallate (CG)	0.4%	0.4%	0 4%

Representative Lots – Tannase-treated GTC

Analysis data for 3 lots of Tannase-treated GTC (Lots: 0512231C, Lots : 0601281C, Lots : 0606181C)

Catechins and Polyphenol	Tannase-treated GTC (Lots :0512231C)	Tannase-treated GTC (Lots :0601281C)	Tannase-treated GTC (Lots :0606181C)
Total Catechin Monomers	62%	62%	63%
Polyphenols	69%	69%	71%
Other components			
Caffeine	1 5%	1.5%	1 3%
Organic acids	1.6%	1.8%	2.1%
Protein and Amino Acids	3 7%	4.4%	3.8%
Saccharide	7.3%	7.3%	6.8%
Fiber	< 0.1%	< 0.1%	< 0 1%
Fat	< 0 1%	< 0 1 %	< 0 1%
Ash	1.2%	1 6%	1.7%
Catechin Profile			
Gallocatechin (GC)	5 9%	5.1%	4.8%
Epigallocatechin (EGC)	20.5%	21.0%	21.0%
Catechin (C)	1 9%	1 9%	1 9%
Epicatechin (EC)	6.2%	5.7%	5 5%
Epicatechin gallate (ECG)	5.0%	5.3%	5.7%
Epigallocatechin gallate (EGCG)	19 8%	20.8%	22 0%
Gallocatechin gallate (GCG)	2 5%	1.6%	1 2%
Catechin gallate (CG)	0.6%	0.5%	0.5%

SUBMISSION END

Reference List for Industry Submission, GRN 000225

Pages	*Author*	*Title*	*Publish Date*	*Publisher*	*BIB_Info*
000136 - 000141	Lane, R.W.; Yamakoshi, J.; Kikuchi, M.; Mizusawa, K.; Henderson, L.; Smith, M.	Safety Evaluation of Tannase Enzyme Preparation Derived from Aspergillus oryzae	1997	Food and Chemical Toxicology	pgs 208 - 212

NA- Not applicable