

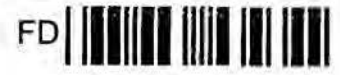


DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
College Park, MD 20740

June 21, 2007



Stephen Paul Mahinka  
Morgan, Lewis & Bockius LLP  
1111 Pennsylvania Avenue, NW  
Washington, DC  
20004

Re: GRAS Notice No. GRN 000225

Dear Mr. Mahinka:

The Food and Drug Administration (FDA) has received the notice, dated May 17, 2007 that you submitted on behalf of Kao Corporation (Kao) in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS)). FDA received this notice on May 18, 2007, filed it on May 24, 2007, and designated it as GRN No. 000225.

The subject of the notice is catechins from green tea extract. The notice informs FDA of the view of Kao that catechins from green tea extract is GRAS, through scientific procedures, for use as an ingredient in beverages, including bottled teas, sport drinks, carbonated soft drinks and juice, at levels according to current good manufacturing practices.

In accordance with proposed 21 CFR 170.36(f), a copy of the information in the notice that conforms to the information described in proposed 21 CFR 170.36(c)(1) is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at <http://www.cfsan.fda.gov/~lrd/foodadd.html>). If you have any questions about the notice, contact me at (301)436-1198.

Sincerely yours,

Negash Belay, Ph.D.  
Division of Biotechnology and  
GRAS Notice Review  
Center for Food Safety  
and Applied Nutrition

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
(b) (5)	(b) (6)				

FILE COPY



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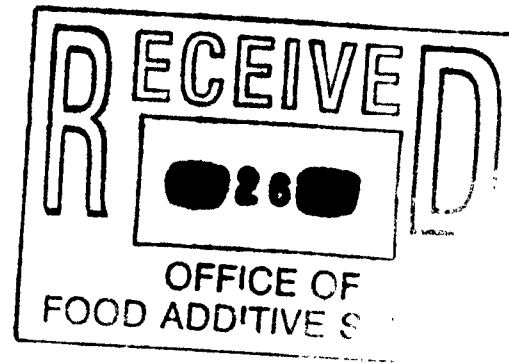
(b) (5)



Morgan, Lewis & Bockius LLP  
1111 Pennsylvania Avenue, NW  
Washington, DC 20004  
Tel: 202.739.3000  
Fax: 202.739.3001  
www.morganlewis.com

**Morgan Lewis**  
C O U N S E L O R S   A T   L A W

**Stephen Paul Mahinka**  
Partner  
202.739.5205  
smahinka@morganlewis.com



November 26, 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, GRAS Notice No. 000225 - Kao Corporation

Dear Sir or Madam:

On behalf of our client, Kao Corporation (Kao), of Tokyo, Japan, we hereby withdraw our GRAS Notice for Green Tea Catechin, filed on May 17, 2007.

Subsequent to the filing of the GRAS Notice, Kao has completed additional clinical studies, which it believes would be useful additions to its GRAS Notice. In addition, Kao is contemplating modifications in the scope of contemplated food uses of its Green Tea Catechin product from those set out in its GRAS Notice.

Consequently, Kao requests that the Agency withdraw its GRAS Notice. Kao likely intends to refile a GRAS Notice for Green Tea Catechin in the future with appropriate additional studies and other modifications.

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Office of Food Additive Safety  
November 26, 2007  
Page 2

Please do not hesitate to contact me if you have any questions.

Sincerely,

A handwritten signature in black ink is completely obscured by two thick, parallel red horizontal lines.

Stephen Paul Mahinka

cc: Negash Belay, Ph.D. (via email)  
Division of Biotechnology and GRAS Notice Review, HFS-255  
Office of Food Additive Safety  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration

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**Belay, Negash**

**From:** Belay, Negash  
**Sent:** Friday, March 28, 2008 2:45 PM  
**To:** 'smahinka@morganlewis.com'  
**Cc:** Gaynor, Paulette M; Martin, Robert L; Chanderbhan, Ronald F; Danam, Rebecca \*; Srinivasan, Jannavi; Dinovi, Michael J  
**Subject:** RE: Kao Corp. GRAS Notice - Summary of Suggestions and Cites

Dear Mr. Mahinka,

In a telephone conversation on November 19, 2007, we discussed with you the status of our review of GRAS Notice No. GRN 000225 GRAS (GRN 225) that was submitted by you on behalf of Kao Corporation (Kao). The subject of the notice is catechins from green tea extract. In that discussion, we informed you that, while our review of the notice was ongoing, we became aware of a report by the United States Pharmacopeia Dietary Supplements Information Expert Committee (USP) that raises safety concerns about the use of green tea catechins. The USP expressed its concern about potential adverse effects of green tea catechins on the liver and proposed a requirement for a cautionary statement on the label of dietary supplement products containing green tea extracts. In light of this development, we informed you of your options with regards to the status of GRN 225 and you indicated that Kao would withdraw the notice and address these safety concerns. We also informed you that we have identified various other insufficiencies in Kao's notice, to be communicated to you at a later time. The withdrawal of Kao's notice was subsequently confirmed by your letter dated November 26, 2007.

On February 29, 2008, you came in for a meeting with us to discuss the additional insufficiencies (i.e., aside from the USP issue) of the withdrawn notice and to inform us about your efforts to address the USP decision. At this meeting you indicated that Kao intends to address all outstanding issues and resubmit the notice. The purpose of this e-mail is, as agreed in our February 29 meeting, to convey to you a compilation of the various additional insufficiencies we identified from our review of GRN 225.

**GENERAL COMMENTS:**

1. No scientific name of the botanical source for the notified substance is provided.
2. Although the subject of the notice is a purified substance, much of the discussion in the notice is about green tea/green tea extract. The discussion needs to be centered on Kao's purified substance and its intended use in food.
3. Kao designates certain information on Page 5 and Pages 8-9 of the notice as confidential. The use of information claimed as undisclosed is inconsistent with GRAS determination criteria.
4. Kao provides publications in Japanese as part of the notice but has not included English translations of those publications.
5. Kao's information on use levels is not clear. A use level of 540 mg per beverage is indicated on page 18 of the notice while a self-limiting use level is also described on page 19.
6. With regard to additional reports (i.e., aside from the USP report) raising safety concerns, those identified below under Toxicology comments are being provided only as examples. Kao needs to address, in a comprehensive manner, all reports in the scientific literature that raise safety concern.

**TOXICOLOGY COMMENTS:**

The 28-day oral (gavage) toxicity studies of Green Tea Catechins (GTC) prepared for beverages in rats evaluated the potential adverse effects of 3 preparations of GTC,

1. Heat sterilized (GTC-H)

2. Unheated(GTC-UH)

3. Decaffeinated (GTC-HDC)

This study reveals the following:

1. At higher doses (1-2g/kg bw/day) of GTC-H, there is a significant decrease in body weight and food consumption, which interestingly, seems to be a distinct effect observed only in the male rats.
2. Similarly, the weights of Spleen, Testis (dose related) Pituitary and Thyroid/Parathyroid glands are significantly reduced in male rats. The authors considered these organ weight differences as spurious, incidental and unrelated to the administration of test articles.
3. In female rats, there is an increase in the weight of Thymus and longer activated chromboplastin time in the decaffeinated and unheated GTC groups respectively.
4. Minimal glandular stomach erosions were observed in both male and female rats (GTC-H).
5. Histological examination of the dead female rat receiving 2g/kg/d GTC-UH revealed extensive necrosis in one liver lobe and mild degenerative changes in the other.

FDA's observations on the 28-day oral (gavage) study:

The changes observed in male rats are consistent with other reports. Since it is a 28 day study and the number of animals in each group is only 5, the significant differences in organ weights will either become more significant or less meaningful in a longer term study with more animals (10-20) per study group. For example, the decrease in food consumption may be correlated to lack of appetite due to changes seen in the endocrine glands. Hence, these differences cannot be ignored.

The minimal glandular stomach erosions appear to be relevant and consistent in the context of gastrointestinal irritation observed in humans consuming high doses of tea preparations.

The authors did not discuss the hepatotoxic effects of GTC although they observe an increase in the Glutamyl transferase activity in female rats.

The following are the possible toxic effects reported by other studies that were not discussed:

1. Several case reports of hepatotoxicity related to the consumption of high doses of tea-based dietary supplements (10-29 mg/kg/d) Ann. Intern. Med. 144, 68-71, 2006.
2. Acute liver failure induced by green tea extracts: case report and review of the literature. Liver Transpl. 2006, 12:1892-5.
3. Cellular and in vivo hepatotoxicity caused by green tea phenolic acids and catechins. Free Rad. Biol. Med. 2006, 40:570-580.
4. A case of hepatotoxicity caused by green tea in a 51-year-old woman from Naples, Italy. Free Radic. Biol. Med. 43, 474, 2007.
5. In vitro hepatotoxicity: Hydro-alcoholic green tea extracts (80% ethanolic dry extracts) at a concentration of 1-3 mg/ml exerted acute cytotoxic effects in rat liver cells. Epigallocatechin-3-gallate (EGCG) was the major contributor to the cytotoxic effect suggesting the hepatotoxic potential of EGCG. The bioavailability and the exposure play a critical role in exerting the toxic effects. Food Chem. Toxicol. 43, 307-314, 2005.
6. Fasting increases the bioavailability of EGCG.
7. The uptake of (-)-Epigallocatechin-3-gallate, (EGCG), the most predominant catechin in GTC is highest and can induce toxicity in the liver, kidneys and intestine.
8. Toxicity in the liver appears to be more predominant in female rats and female dogs (Food Chem. Toxicol. 44, 636-650, 2005).
9. Possibility of individuals with a polymorphism in a key biotransformation pathway for

the tea polyphenols, such as low activity of COMT (catechin-O-methyltransferase) which increases exposure to the unmetabolized parent compound.

10. Involvement and interaction of potentially hepatotoxic pharmaceutical agents such as acetaminophen or other dietary supplements should be considered in humans.

11. Gastric carcinogenesis in rats: This study demonstrates that the combined administration of GTC (1%) and sodium nitrite (0.2%) selectively increased the incidence and multiplicity of neoplastic lesions in the forestomach of the rat after initiation with MNNG (N-methyl-N'-nitro-N-nitrosoguanidine). It also caused significant increases in 8-hydroxyguanosine levels in DNA indicative of oxidative damage. The average daily intakes of GTC were 432-580 mg/kg/day.

The overall data imply that excessive simultaneous intake of green tea and sodium nitrite (dietary nitrate from meats, vegetables and tap water by oral micro flora, food additives) might be a potential human risk, particularly in patients with reflux esophagitis. Cancer Sci 98, 949-957, 2007.

12. Goitrogenic effects: In a 13 week study, goiters were observed in F344 rats administered GTC in their diets. The incidence of thyroid lesions were higher in males than in females. The NOEL of GTC was considered to be 0.625% in males and 1.25% in females, based on histological changes of the thyroid. Arch Toxicol. 75, 591-596, 2001.

13. Teratogenicity and reproductive toxicity:

(a) Tea EGCG, classified as weakly embryotoxic, induces caudal regression in developing rat embryos even at much lower doses. Mal50 =54.2mg/L ; IC50Mal=45.8 mg/L. (Free Radical Biology & Medicine 43: 519-527, 2007) Doses as low as 25 mg/L triggered axial rotational defects and caudal regression and defects in brain and heart. The pro-oxidant effects of EGCG were evident and correlated with increased 8-isoprostane concentrations.

(b) Omitted in Kao's discussion in the notice is also the study by Isbrucker et al.; Safety studies on epigallocatechin gallate (EGCG) preparations. Part 3: teratogenicity and reproductive toxicity studies in rats. This in vivo study reported reduced growth rate in the offspring and slight decrease in the number of pups (even in the 2nd generation). The NOAEL was equivalent to 200 mg/kg/d (including lactating dams). Food Chem. Toxicol. 44:651-61, 2006.

(c) It is also reported that high tea consumption diminishes salivary 17 beta-estradiol concentration in Polish women. Br. J. Nutr. 95:989-995, 2006.

14. Fetal Leukemia Risk:

Dietary flavonoids induce cleavage in the MLL gene and may contribute to infant leukemia. PNAS 97, 4790-4795, 2000.

EGCG was the most abundant catechin in the placenta (3077.4 pmol/g) and the fetus (159.3 pmol/g). Although these levels are much lower than those required to induce chromosomal translocation, further studies are needed in vivo to establish the increased risk, if any, of leukemia due to maternal flavonoid consumption.

Toxicology's overall conclusion:

In light of the above findings, further studies (for example a 90-day study with 10-20 animals/group, peer reviewed & published) or additional scientific information would provide a better understanding of the potential adverse effects of GTC/polyphenols.

CHEMISTRY COMMENTS:

1. Structural Formula of Catechin monomers:

(a) The structure is unclear (is it a C or an O?) - Page 6.

2. Manufacturing Process:

A. Method of Manufacture:



(a) Product description: It varies from Type 1/Type 2, to heated/unheated, to GTC/Tannase-treated GTC to GTC/UT GTC. There needs to be consistency through out the document. The submission also reverses the 'Types' in the discussion (Page 8-9, Page 14-15).

) Unclear if Figure 1 is description of Type 1 process? Also, unclear if Active Carbon in Figure 1 is an 'adsorbing' agent or 'absorbing agent'? - Page 8.

(c) Section III(V) has been referred to in the text along with reference Footnote 18. They do not seem to correlate. Sec III(V) discusses levels of catechin monomers in various tea manufacturing processes while Footnote 18 discusses a 28-day toxicity study with the untreated GTC along with product characteristics for tannase treated GTC- out of place! - Page 9.

(d) Figure 2, Page 9, has speculations such as 'probable' and 'accidental'. Requires rewriting or a method-based LOD specification.

(e) Purity of tannase is 0.9%? - Page 9.

(f) Footnote 17 refers to Section III (E) for 'difference in manufacturing processes'. Notifier describes the differences in product characteristics in that section - Page 9.

### 3. Specifications:

(a) The specification for total catechin monomer is very wide considering the method is HPLC based. Notifier could provide method description - Page 12.

(b) Appendix H: In the three lots' information provided, GTC and Tannase-GTC form 50% and 70%, with 'other components' making 20-30%. What is in the remaining product?

(c) Notifier has set the microbiological and heavy metal specifications for the beverage form. Is the product tested after manufacture and if so what are the manufacturing testing specifications prior to formulation in beverage? - Page 12.

### 4. Analytical methods:

(a) What are the HPLC assays and their specificity in the total catechin monomer method?

(b) How do the JFSL methods compare with standard methods?

(c) Tartaric acid method description is unclear in its purpose and action.

### 5. Product Characteristics:

(a) What is the HPLC method to analyze catechin monomers?

(b) It is unclear as to what the 'derived Na<sub>2</sub>C calorimetric' method is?

(c) The tannase treated GTC seems to have same w/w% of catechins with gallate moiety as the untreated GTC. But the text states that the function of the tannase is to remove these moieties? (Page 9).

(d) Are 'other polyphenols' quantifiable from HPLC? Also, Scale in the figure is not visible.

### 6. Stability in beverages:

(a) GTC in Beverage: Conclusion should be 6 months at 25 deg C and 2 months at 37 deg C not 'for at least 6 months at temperatures up to 37 deg C' - Page 18. (Also, 540 mg total catechin in the product is mentioned here)

'b) Unclear about GTC Type tested in Oolong tea beverage - Page 18

### 7. Self Limiting Levels

(a) Define 'high levels'.

8. Consumption levels and EDI calculation:

(a) Using information through out the document (stability data and footnotes) we gathered the use levels to be 540mg of catechins in 500 ml (max beverage size discussed in the text). Is this correct?

We hope this information is of help to you and contact us again if you have further questions.

Negash

Negash Belay, Ph.D.  
Division of Biotechnology and GRAS Notice Review, HFS-255  
Office of Food Additive Safety  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration

-----Original Message-----

From: smahinka@morganlewis.com [mailto:smahinka@morganlewis.com]  
Sent: Friday, March 07, 2008 9:49 AM  
To: Belay, Negash  
Cc: Kathleen M. Sanzo; Sharon Segal; Dr. Joseph F. Borzelleca  
Subject: Kao Corp. GRAS Notice - Summary of Suggestions and Cites

Negash:

Thank you again for your efforts in arranging what all Kao Corporation representatives believe was a very valuable meeting.

Following our meeting, Kao has confirmed that it definitely intends to refile a GRAS Notice. It intends to refile by the end of March since, as we discussed timing is critical with respect to this product.

Consequently, although we recognize it is a great imposition on your schedule, we would greatly appreciate receiving as soon as possible the brief summary list of the comments and suggestions and of the cites to suggested articles important to include., so that Kao can promptly prepare and submit a new GRAS Notice and Dr. Borzelleca and his panel can prepare a revised Expert Panel Report.

We have, for example, reviewed recent articles for which Lambert is an author, but is difficult for us to determine which ought to be the focus of our consideration as identified by FDA in its prior review.

We greatly appreciate your time in providing this brief summary as soon as possible, so that we might promptly provide a comprehensive and acceptable revised Notice.

Best regards.

Steve

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Sent from my BlackBerry Handheld. (Morgan Lewis)

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