

B

B) SUMMARY OF SCIENTIFIC DATA

1) Green tea consumption estimates

The USDA Continuing Survey of Food Intakes by Individuals⁽¹²⁾ indicates that the mean consumption for all teas including green tea for individuals age 2 and over was 397 grams or 13.4 ounces (1.6 cups), and at the 95th percentile, it was 31.4 ounces (3.9 cups). While fruit and vegetable consumption, which are also sources of the polyphenolic catechins, continue to be suboptimal and fall far short of the five or more servings recommended by the U.S. Dietary Guidelines, the Food Guide Pyramid, and various government reports, the opportunity exists for green tea consumption to make a positive contribution to the cardiovascular health of the American population by reducing some of the risks associated with cardiovascular diseases.

USDA (2003)⁽¹³⁾ recently provided a publicly available database for the flavonoid content of selected foods. It is clear from this information that green tea provides the highest levels of any of the teas of the flavan-3-ols subclass containing the various catechins at meaningful levels on a mg/100 g, edible portion basis. Notably, these levels reported were as follows: EGCG (82.89 mg/100 g), ECG (20.95 mg/100 g), EGC (17.08 mg/100 g), EC (8.5 mg/100 g) and catechin (2.73 mg/100 g). This database also provided information on dried green tea leaves and the catechins' content is actually 10-fold higher. The only other foods providing some degree of catechin contribution of significance were dark chocolate, blackberries and raspberries, but not in the ratios or levels noted for tea. Clearly, dietary green tea sources provide the best venue for consuming the catechin class of polyphenols and obtaining their physiological benefits on a number of cardiovascular risk factors. As will be demonstrated in later sections of this petition, many studies provide evidence for protection against adverse cardiac events by consumption of green tea.

2) Green tea conforms to the definition of "substance" in 21 CFR §101.14(a)(2)

Section 101.70(f) requires that the scientific summary of a health claim petition demonstrate that the substance that is the subject of the proposed claim conforms to the definition of the term "substance" in 21 CFR §101.14(a)(2). Green tea, which is the subject of this claim, meets the definition of a substance under 21 CFR §101.14(a)(2): "a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs or other similar nutritional substances."

3. Clinical and Epidemiological Evidence in Support of the Positive Effects of Green Tea in Lowering Serum Total and LDL-C.

It is well established that elevated total and LDL-C levels are recognized risk factors for cardiovascular disease. Therefore, given this recognition, it is important to address the effect of green tea on reducing these risk factors. A summary of pertinent clinical and epidemiological studies attesting to the positive role of green tea consumption in lowering these risk factors is presented in Table 1.

Lee *et al.* (2005)⁽¹⁴⁾ examined the long-term effects of green tea because of its known antioxidant activity on atherosclerotic biological markers in smokers. Smoking is a known risk factor for coronary disease and triggers vascular injury by platelet aggregation and induces atherosclerosis through induction of oxidative stress. In twenty adult male smokers ingesting 600 mL of green tea daily for 4 weeks, there were significant decreases in both oxidized LDL and also reduced LDL-C. Imai and Nakachi (1995)⁽¹⁵⁾ showed in a population of 1371 men aged over 40 years that increased consumption of green tea (>10 cups/day) was associated with significantly decreased concentrations of total cholesterol and triglycerides and an increased proportion of high density lipoprotein cholesterol. These findings, together with a significant decrease in both low and very low lipoprotein cholesterols, resulted in a decreased atherogenic index. This inverse association between consumption of green tea and various serum risk factors for cardiovascular disease showed the protective effect of green tea. Nakachi *et al.* (2000)⁽¹⁶⁾ also showed in a further study of this population, by segmenting out smokers (766), that serum levels of lipid peroxides were also significantly reduced.

Kajimoto *et al.* (2003)⁽¹⁷⁾ demonstrated in a placebo-controlled double-blind study the blood cholesterol-lowering effect of tea catechins. A green tea beverage containing tea catechins (approx 250 mL beverage containing 197.4 mg of catechins, 328.9 mg tea polyphenols) given twice a day for 12 weeks significantly decreased serum total and LDL-cholesterol (3.5% and 9% respectively) in mild to borderline hypercholesterolemic individuals and the effect appeared to peak at 2 months. Similar and even more striking results were reported in another double-blind randomized, placebo-controlled, parallel-group study by Maron *et al.* (2003)⁽¹⁸⁾ in 240 men and women with mild to moderate hypercholesterolemia. They reported that the administration of a daily capsule containing the flavin-enriched green tea extract (375 mg) for 12 weeks

significantly lowered LDL-cholesterol by 11% and total cholesterol also decreased by 11.3%. In another double-blind placebo-controlled study, Kajimoto *et al.* (2005)⁽¹⁹⁾, investigated the effect of consumption of a catechin-containing tea beverage administered to 196 healthy adults (98 men and 97 women) for 12 weeks either two or three times per day. The beverage (250mL/bottle) contained 215.3 mg of tea catechins, mostly possessing a galloyl moiety, which included EGCG (74.6 mg), ECG (34.1 mg), GCG (77.8 mg), and CG (24.5 mg), all derived from tea extract. The study was conducted as a double-blind study with three parallel groups. The control placebo group received a beverage identical in flavor to the test beverage except that it contained a catechin-free green tea extract. In addition to observing significant decreases in body weight and body mass index (BMI) at both the low and high tea catechin levels, there were significant decreases in total cholesterol (4 and 6.5%) and LDL-C (5.6 and 7.8%) respectively. These data clearly demonstrate a continued decline in these two risk factors of cardiovascular disease with tea catechin treatment and support the earlier work by these investigators and others as noted above. Recently, Erba *et al.* (2005)⁽²⁰⁾ reported similar results of significant LDL-C lowering in subjects consuming 2 cups/day of green tea for 42 days.

Several epidemiological studies have been conducted in a number of different geographic populations in Japan assessing the impact of green tea on serum lipids and cholesterol. Tsubono *et al.* (1997)⁽²¹⁾ did not observe any significant differences in clinical parameters in a cross-sectional study. Others, however, have observed marked positive changes due to green tea consumption. Tokunaga *et al.* (2002)⁽²²⁾ conducted a study of a population of 13,916 (8476 men and 5440 women) aged 40-69 years in the Nagano prefecture. They reported that 87% of the subjects reported daily green tea consumption and that green tea was associated with a significant reduction of total and LDL-C. After adjusting for selected dietary factors, the inverse association remained statistically significant for one cup of green tea/day. In two other cross-sectional studies, Kono *et al.* (1992 and 1996)^(23, 24) also reported significant lowering of total cholesterol and LDL-C in subjects consuming 2 or more cups of green tea/day.

Clearly, the clinical and epidemiological evidence for the positive effect of green tea on total and LDL-Cholesterol lowering in humans provides strong evidence for the requested qualified health claim.

Table 1. Effect of Green Tea on Lowering of Serum Total and LDL-Cholesterol and Triglycerides					
Treatment	N	Design	Duration	Results	References
150 mL GT 4X/day	20-male smokers- Healthy	Intervention	4 wks	Oxidized LDL 17% ↓, (p<.05), no changes in plasma TG, TC, HDL- C, LDL-C	Lee <i>et al.</i> (2005) ⁽¹⁴⁾
GT >10 cups/day	1371 males	Cross Sectional	1986- 1990	TC-5.5% ↓ (p<0.001), TG-12.6% ↓ (p<0.02), LDL-C-1.3% ↓ (p<0.02)	Imai and Nakachi (1995) ⁽¹⁵⁾
250 mL GT 2X/day	60 (38 M, 22 F)	Placebo- Controlled Double Blind	12 wks	TC-5.6% ↓ (p<0.05), LDL-C-9% ↓ (p<0.01), ApoB-3% ↓ (p<0.1), TG and HDL-C unchanged	Kajimoto <i>et al.</i> (2003) ⁽¹⁷⁾
GTE 375 mg	240	Double-Blind Placebo- Controlled Parallel Group	12 wks	TC-11.3% ↓ (p<0.01), LDL-C-16.4% ↓ (p<0.01), TG and HDL-C: N.S.	Maron <i>et al.</i> (2003) ⁽¹⁸⁾
GT:250 mL Beverage 2 or 3 Btls/day	195 M-98 F-97	Double-Blind with 3 Parallel Groups	12 wks	TC-4 & 6.5 % ↓ (p<0.001), LDL-C-5.6 & 7.8% ↓ (p<0.001), TG and HDL-C-N.S.	Kajimoto <i>et al.</i> (2005) ⁽¹⁹⁾
GT: 2-10 cups/day	13,916	Cross Sectional	1995- 1996	TC ↓ (p<0.001) with GT beginning at 1 cup/day; TG and HDL- C :N.S.	Tokunaga <i>et al.</i> (2002) ⁽²²⁾
GT: 1-4+ cups/day	M-634 F-373	Cross- Sectional	1989- 1991	TC, TG, HDL-C-N.S.	Tsubono <i>et al.</i> (1997) ⁽²¹⁾

GT: 0-9 cups/day	1306 males	Cross-Sectional	1986-1988	TC ↓ (p<0.01) at >9 cup/day, TG, HDL-C: N.S.	Kono <i>et al.</i> (1992) ⁽²³⁾
GT: avg. 3.3 cups/day	2062 males	Cross-Sectional	1991-1992	TC and LDL-C ↓ at 10 cups/day (p<0.05), TG and HDL-C: N.S.	Kono <i>et al.</i> (1996) ⁽²⁴⁾
GT: 2 cups/day	24 females	Intervention	42 days	LDL-C ↓ (p<0.05); TC, TG, HDL-C: N.S.	Erba <i>et al.</i> (2005) ⁽²⁰⁾

GT-Green tea; GTE-Green tea extract; TC-Total cholesterol; TG-Triglycerides; HDL-C-High density lipoprotein cholesterol; LDL-C-Low density lipoprotein cholesterol
N.S. Not significant

4. Bioavailability and Pharmacokinetics of Tea Polyphenols

Relevant to the support of the requested qualified health claim for green tea in this petition is the bioavailability of its major active polyphenolic component. An excellent review of polyphenols, their occurrence in foods, and their bioavailability and efficacy in humans have been recently completed by Manach *et al.*, (2005)^(25,26) and Williamson and Manach (2005)⁽²⁷⁾ that included an evaluation of green tea and its catechin components. Their review of research in these articles is summarized below.

It is clear that food components must, by definition, be bioavailable in some form to exert biological effects. There have been major advances in the past few years in our knowledge regarding polyphenol absorption and metabolism (Scalbert and Williamson, 2000⁽²⁸⁾; Manach *et al.*, 2005⁽²⁶⁾), and it is apparent that most classes of polyphenols are sufficiently absorbed to have the potential to exert biological effects. These findings demonstrate that polyphenols cross the intestinal barrier and reach concentrations in the bloodstream that have been shown to exert effects *in vitro*.

As these authors note, there are thousands of articles on the effects of polyphenols on biological systems *in vitro*. However, many of those studies did not take bioavailability and metabolism factors into consideration, and the effects reported in those studies do not necessarily occur *in vivo*. Although most polyphenols are absorbed to some extent, this is very dependent on the type of polyphenol. The range of concentrations required for an effect *in vitro* varies from

<0.1 $\mu\text{mol/L}$ to >100 $\mu\text{mol/L}$. Because physiologic concentrations do not exceed 10 $\mu\text{mol/L}$, the effects of polyphenols *in vitro* at concentrations of >10 $\mu\text{mol/L}$ are generally not valid, with the possible (but unproven) exception of the intestinal lumen. Furthermore, absorption is accompanied by extensive conjugation and metabolism, and the forms appearing in the blood are usually different from the forms found in food. This petition examines the effects demonstrated in some of the intervention studies reported in the literature and present data, which have been excerpted, on green tea and its components. The bioavailability issues for this group of polyphenols are discussed in the context of the intervention studies.

As noted in Section B (1) of this petition, members of the flavonoid group of catechins of interest include Catechin, EGC, ECG, and EGCG. (+)-Catechin and EC are widely distributed in foods. Catechin concentrations are especially high in broad beans, black grapes, apricots, and strawberries. EC is found at high concentrations in apples, blackberries, broad beans, cherries, black grapes, pears, raspberries, and chocolate. The gallates and the gallocatechins, which are the focus of this petition, are found almost exclusively in tea, especially green tea. Deducing the intake of catechins during intervention studies is more difficult because the non-galloylated forms are widespread and can complicate intake estimates. This can lead to consumption of additional sources of catechins; furthermore, the amounts consumed were not always measured. The situation is clearer for the gallates or galloylated catechins, because they are almost exclusive to green tea, and the amounts of remaining monomeric catechins can be readily estimated. Catechins are biologically active molecules that have a wide range of effects *in vitro*.

5. Human Intervention Studies with Green Tea

In human intervention studies (Table 2) adapted from Williamson and Manach (2005)⁽²⁷⁾, catechins in green tea increased plasma antioxidant activity as assessed with a variety of assays, decreased plasma lipid peroxide and malondialdehyde concentrations, increased plasma ascorbate concentrations, decreased nonheme iron absorption, and increased the resistance of LDL to oxidation. In addition, the green tea catechins, including the galloylated catechins, increased fat oxidation and energy expenditure and decreased the respiratory quotient and body weight.

Substances Given	Principal Polyphenols ²	Dose Per Day	Days	No. of Subjects/ Group ³	Biomarkers Significantly Affected	Biomarkers Not Significantly Affected	Reference
Black tea, green tea, polyphenol-rich extract	Catechins	900 mL	28	13-16		Serum interleukin-6, interleukin-1 β , tumor necrosis factor- α , C-reactive protein, fibrinogen, plasminogen activator inhibitor-1, LDL oxidation, plasma cholesterol or triglycerides, plasma vitamin C or E	deMaat et al (2000) ⁽²⁹⁾ , Princen <i>et al.</i> (1998) ⁽³⁰⁾
Green tea	Catechins	5 g of green tea	1		Plasma ascorbic acid increased	Plasma β -carotene, α -tocopherol, uric acid	Gomikawa and Ishikawa (2002) ⁽³¹⁾
Green tea drink	Catechins	150, 300, 450 mL	1	10	Dose-dependent increase in plasma antioxidant activity		Sung <i>et al.</i> (2000) ⁽³²⁾
Green tea extract	Catechins	254 mg total catechins	1	18	40% decrease in plasma phospholipids hydroperoxide levels		Nakagawa <i>et al.</i> (1999) ⁽³³⁾
Green tea, black tea	Catechins	8 cups	3	18		LDL oxidation ex vivo	van het Hof <i>et al.</i> (1999) ⁽³⁴⁾
Green tea extract	Catechins	90 mg EGCG	1	10	Energy expenditure 4% higher, respiratory		Dulloo <i>et al.</i> (1999) ⁽³⁵⁾

1 ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule.

2 The measured polyphenol; the dose is given in the next column.

3 Healthy subjects, unless otherwise stated.

The amounts of catechins administered in various intervention studies were highly variable, and administration was for short periods (1–28 d) (Table 2). With a dose of epigallocatechin gallate (EGCG) of 50 mg, peak plasma concentrations were $\sim 0.15 \mu\text{mol/L}$ (Manach *et al.*, 2005)⁽²⁶⁾. Although the exact percentages vary among individuals, among different studies, and with time after consumption, a substantial amount of the EGCG in plasma is unconjugated. For example, EGCG given to volunteers in one dose of 2 mg/kg body wt yielded 77% of total EGCG as the unconjugated form at 1 h after consumption, with some individuals exhibiting values as high as 100% (Lee *et al.*, 2002)⁽⁴⁴⁾. Earlier work by Nakagawa *et al.* (1997)⁽⁴⁵⁾ demonstrated that green tea catechins administered as a green tea extract to healthy human subjects at doses of 225, 375, and 525 mg EGCG and 7.5, 12.5, and 17.5 mg EGC, respectively showed a dose-dependent increase in plasma with levels of 0.2–2.0% of the ingested amount detected. Chow *et al.* (2001)⁽⁴⁶⁾ compared the pharmacokinetics and systemic availability of green tea catechins after a single oral dose administration of EGCG or Polyphenon E (decaffeinated green tea mixture) in a cross-over study in 20 healthy subjects receiving 200, 400, 600, and 800 mg based on EGCG content. The two catechin formulations resulted in similar plasma EGCG levels and pharmacokinetics. In the case of the Polyphenon E administration, high concentrations of EGC and EC glucuronide/sulfate conjugates were observed in plasma and urine. Chow *et al.* (2003)⁽⁴⁷⁾ also conducted a safety and pharmacokinetics evaluation after 4 weeks of oral administration of EGCG and Polyphenon E at doses of 800 mg EGCG once per day, 400 mg EGCG twice/day, 800 mg EGCG as Polyphenon E once/day, and 400 mg EGCG as Polyphenon E twice/day. There was a >60% increase in the systemic availability of free EGCG after chronic green tea polyphenol administration from the high daily bolus dose (800 mg EGCG or Polyphenon E once daily). It was concluded that it is safe for healthy individuals to take green tea polyphenol products in amounts equivalent to the EGCG content in 8–16 cups of green tea once/day or in divided doses twice a day for 4 weeks.

In summary, the intervention studies with monomeric catechins give rise to plasma concentrations on the order of 0.1–0.5 $\mu\text{mol/L}$, but with rapid clearance. Substantial amounts of unconjugated forms of EGCG would be present in plasma, but all (+)-catechin and (–)-

epicatechin is predicted to be conjugated. The percentage of catechins in the plasma that are sulfated or glucuronidated depends on the dose, but this is not usually measured in intervention studies.

6. Antioxidant Properties of Green Tea

The potential for green tea, through its antioxidant components, to reduce the risk of certain risk factors of cardiovascular disease has been of great interest to investigators. Benzie *et al.* (1999)⁽⁴⁸⁾ demonstrated that consumption of green tea causes a rapid increase in plasma antioxidant power (within 40 minutes of consumption). Pietta *et al.* (1998)⁽⁴⁹⁾ administered green tea catechins to humans as either free catechins (400 mg equivalent to 2-3 cups of green tea) or the same amount in a phospholipids complex and showed that the phospholipids complex was absorbed more extensively, although the extent does not exceed 2 % of the dose. Further, this single dose of green tea catechins induced a transient decrease of plasma ascorbate, and total glutathione and plasma antioxidant status was increased. Miyazawa (2000)⁽⁵⁰⁾ in a minireview on this subject noted that the level of green tea catechins in plasma of subjects consuming green tea or green tea extract can reach a maximum plasma concentration of 4400 pmol/mL and that this would be sufficient to achieve antioxidative effects in the blood stream. Further, phosphatidylcholine hydroperoxide, a marker of oxidative injury of plasma proteins, is lowered in humans after green tea catechin supplementation. This decrease correlates with increases in plasma EGCG. This beneficial effect of EGCG from green tea could, in part, be mediated through protection of oxidative modification of plasma proteins. *In vivo* evidence for antioxidant activity of green tea polyphenols is also provided from animal studies as noted in reviews by Frei and Higdon (2003)⁽⁵¹⁾ and Higdon and Frei (2003)⁽⁵²⁾. Tea polyphenols act as antioxidants *in vitro* by scavenging reactive oxygen and nitrogen species and chelating redox-active metal ions. They may also function indirectly as antioxidants through inhibition of redox-sensitive transcription factors, inhibition of pro-oxidant enzymes such as inducible nitric oxide synthase, lipoxygenases, cyclooxygenases and xanthine oxidase, and by induction of phase II and antioxidant enzymes such as glutathione S-transferases and superoxide dismutases. Indeed, in animal models, green and black tea administration has shown modest improvements in the resistance of lipoproteins to *in vivo* oxidation.

Langley-Evans (2000)⁽⁵³⁾ showed that the maximum antioxidant capacity from green tea is obtained by infusion with water at 90° C for up to 2 minutes and when taken with either fat-free milk or without milk addition. Leenen *et al.* (2000)⁽⁵⁴⁾ showed in human volunteers that a single dose of green tea, with or without milk, induces a significant rise in plasma antioxidant activity *in vivo*. Sung *et al.* (2000)⁽³²⁾ also demonstrated the *in vivo* antioxidant effect of green tea over a 3-week period in human subjects. Total plasma antioxidant activity was significantly increased 7 % after 60 min and 6.2% after 120 min after taking green tea in amounts of 300 mL, and 12 % after 60 min and 12.7% after 120 min after consuming 450 mL. A number of other studies have also examined the effect of green tea or green tea extract on plasma antioxidant capacity in humans and these are shown in Table 3. In each case, the data in this Table show that there is an increase in time to oxidation in subjects consuming green tea, adding support to the efficacy of green tea's antioxidant function.

Table 3. Effects of Green Tea or Its Catechins on Plasma Antioxidant Capacity and Susceptibility to Oxidation

Treatment	N	Design	Assay	Results	Reference
300 mL Green Tea	5	Crossover between tea with and without milk	TRAP	Green tea:40% increase over baseline	Serafini <i>et al.</i> (1996) ⁽⁵⁵⁾
900 mL green tea/day x 4 wk	14	Parallel	TEAC	3.5% increase	Van het Hof <i>et al.</i> (1997) ⁽⁴²⁾
300 ml green tea	6	Compared after 1-5 hr after ingestion to baseline	TRAP (ORAC)	15% increase	Pietta <i>et al.</i> (1998) ⁽⁴⁹⁾
400 mg green tea catechins with and without phospholipids	6	Parallel; compared 180 minutes after ingestion to baseline	TRAP (ORAC)	Free: 16% increase at 4 hr post ingestion;Phospholipid: 19% increase at 180 min post ingestion	Pietta <i>et al.</i> (1998) ⁽⁴⁹⁾

Table 3. Effects of Green Tea or Its Catechins on Plasma Antioxidant Capacity and Susceptibility to Oxidation					
Treatment	N	Design	Assay	Results	Reference
300-400 mL strong green tea	10	Crossover	FRAP	Green tea higher than control at 20, 40, 60 min after ingestion	Benzie <i>et al.</i> (1999) ⁽⁴⁸⁾
150, 300, 450 mL green tea	10 10 10	Complete crossover compared baseline to 60 min after ingestion	TEAC	150 mL; no increase; 300 mL: 7% increase at 60 min and 6% increase at 120 min; 450 mL: 12% increase at 60 min and 120 min	Sung <i>et al.</i> (2000) ⁽³²⁾
400 mL green tea	20	Complete crossover; compared baseline to 60 min after ingestion	TRAP	Nonsignificant increase of 4% compared to black tea (3%)	Hodgson <i>et al.</i> (2000) ⁽³⁷⁾
300 mL green tea with and without milk	21	Complete crossover; compared baseline to 60, 90, 120 min after ingestion	FRAP	Green tea: 3% increase compared to water; greater than black tea at all times; milk did not alter response	Leenen <i>et al.</i> (2000) ⁽⁵⁴⁾
300 mL green tea	5	Complete crossover; compared baseline to 30, 50, 80 min after ingestion	TRAP (ORAC)	Green tea: 40% increase from baseline at 30 min, 20% increase at 50 min	Serafini <i>et al.</i> (2000) ⁽⁵⁶⁾
1 green tea extract	4	Compared	Cu-	PCOOH 69% lower at	Nakagawa

Treatment	N	Design	Assay	Results	Reference
tablet containing EGCG:82 mg, ECG:38 mg, EC: 33 mg, EGC:27 mg, GCG: 37 mg		plasma oxidation before and 60 min after ingesting green tea	mediated plasma oxidation; PCOOH & TBARS formation	45 min oxidation after green tea extract; TBARS 72% lower at 180 min oxidation after green tea extract	<i>et al.</i> (1999) ⁽³³⁾
400 mL green tea	20	Complete crossover Compared serum oxidation 90 min after beverage	Cu-mediated serum oxidation; Conjugated diene formation	Compared with water, green tea increased lag time by 4.4 min	Hodgson <i>et al.</i> (2000) ⁽³⁷⁾

TRAP: Total peroxy radical trapping assay

ORAC: Oxygen radical absorbance capacity assay

FRAP: Ferric reducing ability of plasma assay

TEAC: Trolox-equivalent antioxidant capacity assay

PCOOH: phosphatidylcholine hydroperoxide

TBARS: Thiobarbituric acid reactive substances

7. Effects of Green Tea and Its Catechins on LDL-Cholesterol Oxidation and Endothelial Function in Humans

It is well known that oxidative stress and modification of low-density lipoprotein is thought to play a key role in the processes involved in changes that occur in the arterial wall leading to atherogenesis. Equally, there is a keen interest in the antioxidant properties of green tea and its catechin components as effective protectants against LDL oxidation. The catechin content of green teas correlates with their antioxidant activity (Henning *et al.*, 2003)⁽⁵⁷⁾.

Luo *et al.* (1997)⁽⁵⁸⁾ showed *in vitro* that green tea extract effectively inhibited LDL oxidation at a dose as low as 0.25 $\mu\text{mol/L}$. Similar findings were reported by Yokozawa and Dong (1997)⁽⁵⁹⁾ for green tea and its polyphenols. Osada *et al.* (2001)⁽⁶⁰⁾ demonstrated *in vitro* that tea catechins inhibit cholesterol oxidation accompanying oxidation of low density lipoprotein. Both EGCG and ECG inhibited the formation of oxidized cholesterol and decreased linoleic and arachidonic acids in copper-catalyzed LDL oxidation, indicating that they functioned by a combination of interference with polyunsaturated fatty acid (PUFA) oxidation, reduction and scavenging of copper ion and hydroxyl radical generated from peroxidation of PUFA and superoxide anion. Zhu *et al.* (1999)⁽⁶¹⁾ showed that green tea catechins provide a dose-dependent protective activity to α -tocopherol in LDL, resulting in a regeneration of α -tocopherol.

Apolipoprotein B-100 (apoB) has been identified as a marker of atherogenic activity. Hashimoto *et al.* (2000)⁽⁶²⁾ also reported that the green tea catechins are significant antioxidants and significantly inhibit the radical reaction of apoB proteins and α -tocopherol in human plasma, which can be an effective indicator of anti-atherogenic activity. Yee *et al.* (2002)⁽⁶³⁾ conducted *in vitro* studies to evaluate the efficacy of EC and EGCG on apoB and lipid production using the well established hepatoma cell line, HepG2. EGCG was shown to be a potent inhibitor of apoB secretion via a proteasome-independent pathway, suggesting a beneficial effect on lipid metabolism. Tedeschi *et al.* (2002)⁽⁶⁴⁾ demonstrated that EGCG inhibited the expression of genes typically involved in inflammatory processes. Bursill *et al.* (2001)⁽⁶⁵⁾ showed that green tea upregulates the LDL receptor through the sterol-regulated element binding protein in HepG2 liver cells; therefore this LDL receptor may play a role in the hypocholesterolemic effect of green tea. Kuhn *et al.* (2004)⁽⁶⁶⁾ showed that green tea polyphenols containing ester bonds inhibit the ubiquitin proteasome-mediated degradation of the active form of the sterol regulatory element-binding protein, an essential factor for LDL receptor transcription, resulting in up-regulation of the LDL receptor. Jiao *et al.*, (2003)⁽⁶⁷⁾ reported that green tea polyphenols provide a protective effect against the cytotoxic effects of the hypolipidemic agent fenofibrate, and that it may be beneficial for patients to drink green tea synchronously during their treatment.

Elevated plasma levels of LDL have been implicated in the pathogenesis of atherosclerotic disease. Locher *et al.* (2002)⁽⁶⁸⁾ demonstrated that green tea polyphenols inhibit human vascular smooth muscle proliferation stimulated by native LDL and thus may exert vascular protection by inhibiting human vascular smooth muscle cell growth associated with

hypercholesterolemia. Dona *et al.* (2003)⁽⁶⁹⁾ showed that decaffeinated green tea represses reactive oxygen species activity and inhibits apoptosis of activated neutrophils. Green tea also dramatically inhibited chemokine-induced neutrophil chemotaxis *in vitro*; further, oral EGCG and green tea extract blocked neutrophil-mediated angiogenesis *in vivo* in an inflammatory angiogenesis model and oral administration of green tea extract enhances resolution in a pulmonary inflammation model by significantly reducing consequent fibrosis. All of these observations support green tea's therapeutic potential to reduce the risk of factors leading to cardiovascular disease.

The inhibitory effect of Chinese green tea on endothelial cell-induced LDL oxidation was shown by Yang and Koo (2000)⁽⁷⁰⁾ *in vitro* in human umbilical cord endothelial cells, further supporting the hypothesis that green tea may delay atherogenesis. Lu *et al.* (1998)⁽⁷¹⁾ suggested that the antiproliferative effect of EGCG on vascular smooth muscle cells may be mediated through inhibition of protein tyrosine kinase activity, reducing and inhibiting activation. Maeda *et al.* (2003)⁽⁷²⁾ provided data supporting the anti-invasive effect of green tea catechins (mainly EGCG) on migration of smooth muscle cells through the basement barrier of the endothelium, as well as their effect on inhibiting the metalloproteinase activities, as partially supportive of the anti-atherogenic action of catechin. Nagaya *et al.* (2004)⁽⁷³⁾ showed in healthy smokers (N=20) that green tea reverses endothelial dysfunction by vasodilatation, possibly through its antioxidant effect. Zheng *et al.* (2004)⁽⁷⁴⁾ showed that EGCG directly inhibited angiotensin II, which is known to stimulate vascular smooth muscle cell hypertrophy and this inhibition occurs specifically at the protein tyrosine kinase level, providing further support for green tea's beneficial effect on cardiovascular disease by lowering the rate of vascular smooth muscle hypertrophy.

8. Effect of Green Tea on Regulation of Specific Genes Involved in Atherosclerosis

The genomics of atherosclerosis and the role of the genes that code for the LDL-receptor, and thus lipid metabolism, as well as cytokine production and cellular activity within the arterial wall, were recently examined by Kaul *et al.* (2004)⁽⁷⁵⁾. Green tea polyphenols were shown to effectively down-regulate and up-regulate specific genes involved in the atherosclerotic process at the transcriptional level. Based on these findings, the authors proposed that green tea polyphenols have the inherent capacity to inhibit the development of atherosclerotic lesions. Hofmann and Sonenshein (2003)⁽⁷⁶⁾ also provided evidence for a new molecular mechanism

whereby green tea polyphenols inhibit smooth muscle cell proliferation and function to prevent the development of atherosclerosis. Green tea polyphenols and EGCG were shown to slow smooth muscle cell growth in a dose-dependent fashion and EGCG specifically induced apoptosis in proliferating smooth muscle cells.

9. Effect of Green Tea and its Components on Platelet Function and the Inflammation Process

Platelets play an important role in normal hemostasis and in thrombosis at the site of damaged blood vessels. The inhibition of platelet aggregation is therefore of concern in the effective treatment of thrombosis in cardiovascular disorders. Early work by Sagesaka-Mitane *et al.* (1990)⁽⁷⁷⁾ demonstrated experimentally in rabbit platelets that tea catechins are active principles for inhibition of collagen-induced platelet aggregation and that ester-type catechins (EGCG) are more effective than free-type catechins. Kang *et al.* (1999)⁽⁷⁸⁾ showed that green tea catechins and its EGCG component inhibited human platelet aggregation *in vitro* and the mode of antithrombotic action appears to be due to their antiplatelet activities, not anticoagulation activities. Kang *et al.* (2001)⁽⁷⁹⁾ further reported that the antiplatelet activity of green tea extract was mediated by inhibition of cytoplasmic calcium increase, which leads to the inhibition of fibrinogen-human platelet glycoprotein (GPIIb/IIIa) binding via activation of Ca^{2+} -ATPase and inhibition of inositol 1,4,5-triphosphate (IP_3) formation. Paquay *et al.* (2000)⁽⁸⁰⁾ further demonstrated *in vitro* the protective effects of green tea polyphenols on nitric oxide toxicity with green tea scavenging nitric oxide, thus inhibiting the excessive production of nitric oxide and suppressing the induction of nitric oxide synthase. Nitric oxide is produced by the endothelium of cerebral arteriolar resistance vessels and is an important mediator of the endothelium. Too much nitric oxide results in the formation of peroxynitrite, which is able to initiate oxidation of LDL, a key event in the etiology of atherosclerosis. Nakagawa and Yokozawa (2002)⁽⁸¹⁾ showed the direct scavenging of nitric oxide by the spectrum of catechins that make up green tea, with EGCG, GCG and ECG having the highest scavenging activities. They also showed the importance of the structure of the flavan-3-ol linked to gallic acid for this activity. Lorenz *et al.* (2004)⁽⁸²⁾ demonstrated the mechanism, whereby EGCG activates endothelial nitric oxide synthase leading to endothelial-dependent vasodilation. Lee *et al.* (2005)⁽¹⁵⁾ measured biological markers for atherosclerosis including P-selectin in smokers before, and 2 and 4 weeks after, green tea ingestion (600mL) to examine the effect of green tea ingestion on *in vivo* vascular inflammatory responses. P-selectin plasma concentration reflects platelet activation and was

decreased by 55% after 4 weeks of green tea ingestion. A significant decrease was also observed in oxidized LDL.

It was reported by de Maat *et al.* (2000)⁽⁸³⁾ that consumption of green tea had no effect on inflammation, hemostasis and endothelial markers in smoking, healthy subjects. In addition, while Princen *et al.* (1998)⁽³⁰⁾, van het Hof *et al.* (1997, 1999)^(34, 42) and Hodgson *et al.* (2000 and 2002)^(37, 38) reported that green tea did not affect lipoprotein oxidation *in vitro* or lipid peroxidation and LDL oxidation *in vivo or ex vivo* in humans, there are several other studies that have reported a positive effect for green tea on prevention of oxidative modification of low density lipoproteins. Miura *et al.* (2000)⁽⁸⁴⁾ showed that green tea polyphenols (300 mg green tea polyphenol extract daily/7 days) render LDL resistant to *ex vivo* oxidation in humans. The lag time increased 20% in the green tea extract group. This was equivalent to 7-8 cups (approximately 100 mL each cup) of green tea. Serafini *et al.* (2000)⁽⁵⁶⁾, as reported earlier, showed that green tea significantly raised the plasma antioxidant activity. Recently, Erba *et al.* (2005)⁽²⁰⁾ demonstrated that the addition of 2 cups/day of green tea (approximately 250 mg catechins) for 42 days to a healthy group of volunteers resulted in a significant increase in plasma antioxidant activity, significant decreases in plasma peroxides, a moderate, although significant, decrease in LDL-C and a significant increase in the resistance to lymphocyte DNA damage. These results support the ability of green tea to improve overall antioxidant status and to protect against oxidative damage in humans.

10. Effect of Green Tea on Blood Pressure and Hypertension

There are a limited number of studies in the literature on the effect of drinking green tea on blood pressure and hypertension. Hodgson *et al.* (1999)⁽⁸⁵⁾ investigated the effects on blood pressure in a limited study (13 subjects) with high-normal systolic blood pressure and mild systolic hypertension by measuring 24 hr ambulatory pressure after consumption of 5 cups of green tea per day for 7 days and found no significant alterations. Yang *et al.* (2004)⁽⁸⁶⁾ reported on the protective effect of habitual green tea consumption by examining the effect of green tea drinking on the risk of newly diagnosed hypertension in 1507 subjects (711 men and 796 women), age 20 or older who did not have a hypertensive history. They reported that, in 600 subjects (39.8% of this sample), who were habitual tea drinkers as defined by tea consumption of 120 mL/day or more for at least a year, the risk of developing hypertension decreased by 46% for

those who drank 120 to 599 mL/day, and was further reduced by 65% for those who drank 600 mL or more, after carefully adjusting for a host of other factors.

11. Other Human Studies and Clinical Trials on Green Tea and Cardiovascular Disease

As noted earlier, the literature is replete with epidemiologic studies suggesting that consumption of green tea and its catechins can effectively reduce the risk of cardiovascular disease. Similarly, there are multiple reviews on the health promoting properties of tea and its polyphenols in optimizing health. (Mukhtar and Ahmad, 2000⁽⁸⁷⁾; Vinson, 2000⁽⁸⁸⁾; Dufresne *et al.* 2001⁽⁸⁹⁾; Sueoka *et al.*, 2001⁽⁹⁰⁾; Riemersma *et al.*, 2001⁽⁹¹⁾; and Yang, (2004)⁽⁸⁶⁾.

The onset of lifestyle-related diseases such as cardiovascular disease depends on slowing the aging process and the appearance of diseases that follow. Nakachi *et al.* (2003)⁽⁹²⁾ analyzed data from a prospective cohort study of a Japanese population with 13-year follow-up data on the association between age at cardiovascular death and consumption of green tea and reported that, in those consuming the largest amounts (>4 cups/day), subjects consistently showed later ages at cardiovascular death. Hertog *et al.* (1995)⁽⁹³⁾ reported on flavonoid intake and long-term risk of coronary heart disease in the Seven Countries Study and noted that average intake of antioxidant flavonoids was inversely associated with mortality from coronary heart disease. The Rotterdam Study was a population-based prospective, 3-year study of 7983 men and women 55 years or older that assessed dietary tea intake and atherosclerosis (Geleijnse *et al.*, 1999)⁽⁹⁴⁾. Multivariate analyses showed a significant inverse association of tea intake and severe aortic atherosclerosis. Odds ratios decreased from 0.54 (95% CI, 0.32-0.92) for drinking 125 to 250 mL (1-2 cups) of tea to 0.31 (CI, 0.16-0.59) for drinking more than 500 mL/day (4 cups/day) and the association was stronger in women than men. All these data emphasize the importance of the protective effects of tea flavonoids against oxidation of LDL and the development of fatty streaks. The Zutphen Elderly Study (Hertog *et al.* (1993, 1995)^(93, 95) was a five year prospective cohort study of 806 men aged 65-84 that showed a 50% reduced risk in mortality. A follow-up of this study evaluating catechin intake and ischemic heart disease, (Arts *et al.*, 2001)⁽⁹⁶⁾ showed that catechin intake was inversely associated with ischemic heart disease mortality; the multivariate-adjusted risk ratio in the highest tertile of intake was 0.49 (95% CI: 0.27, 0.88; P=0.017). Catechin intake was not associated with the incidence of myocardial infarction, but after adjusting for tea consumption and flavonol intake, a 7.5 mg increase in catechin intake from other sources than

tea was associated with a 20% reduction in ischemic heart disease mortality risk ($P=0.114$). No association was observed between catechin intake and stroke incidence or mortality. No protective effect of tea and flavonoids against coronary events was observed in the male cohorts of the Health Professionals Follow up Study (Rimm *et al.*, 1996)⁽⁹⁷⁾, but a second analysis of the data found that flavonoid intake was associated with a lower risk of coronary mortality only among men with prevalent cardiovascular disease. A prospective cohort study of 1900 patients hospitalized with a confirmed acute myocardial infarction, with a median follow-up of 3.8 years, was performed by Mukamal *et al.* (2002)⁽⁹⁸⁾. Compared with non-tea drinkers, age- and sex-adjusted mortality was lower among moderate tea drinkers (<14 cups/week; hazard ratio, 0.72; 95% CI, 0.53 to 0.89) and heavy tea drinkers (>14 cups/week; hazard ratio, 0.61; 95% CI, 0.42 to 0.86). Self-reported tea consumption in the year before acute myocardial infarction was associated with lower mortality after infarction.

Nakachi *et al.* (2000)⁽¹⁷⁾ conducted a followup prospective cohort study on a total of 8,552 individuals to estimate the relative risk of death. Men consuming over 10 cups/day had a significantly decreased risk ratio of 0.58, adjusted for lifestyle factors, and interestingly, high consumption of green tea lowered the risk of cardiovascular death even among smokers (RR, 0.51). Ten cups (150 mL/cup) of green tea contains 360-540 mg of EGCG or about 1 gram of tea polyphenols, which is thought to be the required daily amount for prevention of cardiovascular disease. Examining cumulative survival by consumption of green tea indicated a significant increase of percent survivors in both men and women consuming over 10 cups of green tea per day compared to those consuming smaller amounts.

Sasazuki *et al.* (2000)⁽⁹⁹⁾ evaluated 838 patients aged 30 years or older who underwent coronary arteriography for the first time in their life in a prospective study. Green tea consumption tended to be inversely associated with coronary atherosclerosis in men, but not in women. An evident, protective association between green tea and coronary atherosclerosis was observed in a subgroup of 262 men, excluding those under dietary or drug treatment for diabetes. In this subgroup, after adjustment for traditional coronary risk factors and coffee, odds ratios of significant stenosis for consumption of 2-3 cups and 4 or more cups of green tea per day were 0.5 (95% CI, 0.2-1.2) and 0.4 (0.2-0.9), respectively, as compared with consumption of one cup or less of tea. Hirano *et al.* (2002)⁽¹⁰⁰⁾ conducted a prospective study in 393 Japanese patients who had coronary angiography for suspected coronary artery disease and consumption of green

tea. They did not find any inverse relationship between green tea and coronary artery disease. However, myocardial infarction was significantly less prevalent in green tea drinkers than in nondrinkers. A green tea intake of ≥ 1 cup/day was found to be inversely associated with myocardial infarction. Cheng (2003)⁽¹⁰¹⁾ proposed that the reason for Hirano et al (2002)⁽¹⁰⁰⁾ observation of decreased myocardial infarction is due to the anti-inflammatory properties of green tea and its polyphenols through its antioxidant effects on the inflammatory process.

Sano *et al.* (2004)⁽¹⁰²⁾ recently conducted a prospective study of 203 patients in Japan who underwent elective coronary angiography (109 patients with significant coronary stenosis and 94 without). Green tea consumption was significantly higher in patients without coronary disease than in those with it (5.9 ± 0.5 vs 3.5 ± 0.3 cups/day; $P < 0.001$). An inverse relationship between the intake of green tea and the incidence of coronary artery disease was observed ($P < 0.001$). The green tea intake per day was an independent predictor for coronary artery disease based on a multivariate logistic regression analysis (odds ratio: 0.84 and 95% confidence interval: 0.76-0.91). Green tea was not a predictor of cardiovascular or cerebrovascular events.

From the foregoing information, there is a wealth of published data supporting the positive effect of green tea and its catechins in reducing the risk of factors associated with cardiovascular disease.

12. Conclusions on Available Scientific Data

The bioavailability and pharmacokinetics of the green tea catechins reviewed above clearly demonstrate that they are rapidly absorbed, crossing the intestinal lumen and reaching peak plasma levels within 2 hours, which have been demonstrated to exert positive biological effects *in vitro*. They are also rapidly cleared from the body. The green tea and catechin intakes investigated in the intervention studies discussed above (see Tables 1, 2 and 3 and the accompanying section on clinical trials) covered a broad spectrum of intake from 1-10 cups of green tea, providing approximately 125 mg to 1 gram catechins per day. The studies of Hertog *et al.* (1993 and 1995)^(93,95) showed an inverse association between flavonol intake and cardiovascular disease in Europe. The Zutphen Elderly Study provided strong epidemiological evidence from a 10-15 year follow-up for an inverse relationship between flavonol intake and coronary heart disease. Consistent with these observations, an inverse correlation between flavonol intake and CHD mortality was observed in the Seven Countries Study. Rimm *et al.*

(1996)⁽⁹⁷⁾ reporting on the Health Professional Health study found a lower risk of coronary mortality with increased flavonoid intake. The protective effect of green tea against cardiovascular diseases has been documented in several studies conducted in Japan. The authors of a recent meta-analysis (Peters et al, 2001)⁽¹⁰³⁾ of 10 cohort and 7 case control studies concluded that an increase in tea consumption of 3 cups (711 ml/day) decreased the risk of myocardial infarction by 11%. Imai and Nakachi (1995)⁽¹⁵⁾ showed that consumption of green tea, especially more than 10 cups (about 1500 mL/day), significantly decreased total cholesterol, LDL-cholesterol, serum lipid peroxide levels, and triglycerides in smokers. Kono *et al.* (1992, 1996)^(23,24) reported similar observations. Nakachi et al (2000)⁽⁹⁶⁾, in a follow-up to the Imai study, found that green tea significantly lowered the risk of cardiovascular death and increased percent survival. Geleijnse *et al.* (1999)⁽⁹⁴⁾ reported in the prospective Rotterdam study that 1-2 daily cups of tea lowered aortic atherosclerosis. Sasazuki *et al.* (2000)⁽⁹⁹⁾ reported that 2-3 cups or 4 or more cups of green tea significantly lowered stenosis. Hirano et al (2002)⁽¹⁰⁰⁾ found that myocardial infarction was significantly lowered with consumption of greater than 1 cup of green tea/day. Sano *et al.* (2004)⁽¹⁰²⁾ reported a significant inverse relationship between green tea intake and coronary disease.

The antioxidant potential of green tea and its catechins has been well established, as noted in Table 3 both *in vitro* and *ex vivo* in a number of studies, as evidenced by increases in the lag time of low density lipoprotein oxidation. Also shown in a number of *in vitro* experiments referenced in this petition, green tea and its catechin components have a pronounced effect on endothelial function, vasodilatation, platelet aggregation, inflammation and nitric oxide toxicity. The recent findings of Erba *et al.* (2005)⁽²⁰⁾ clearly demonstrated that the ingestion of 2 cups/day of green tea (approximately 250 mg catechins) resulted in a significant increase in plasma antioxidant activity, significant decreases in plasma peroxides, a moderate but significant decrease in LDL-cholesterol and a significant increase in the resistance to lymphocyte DNA damage. The placebo-controlled double-blind studies of Kajimoto *et al.* (2003)^(17,19) and Maron et al (2003)⁽¹⁸⁾, along with several significant epidemiological studies noted in Table 1, provide ample evidence for the significant positive lowering effects of green tea on total and LDL-cholesterol, two well recognized risk factors for cardiovascular disease. The consistent reproducibility of these latter studies provides strong and meaningful evidence to support a

qualified health claim for green tea and its role in reducing several key risk factors associated with the onset of cardiovascular disease.

Taken together, a growing body of evidence has provided substantive clinical and mechanistic information about how green tea and its polyphenols can reduce risk factors associated with cardiovascular disease. These data also provide additional evidence for a biological effect of polyphenols in green tea, rather than a simple association of polyphenol intake with a healthier lifestyle or other confounding factors (Vita, 2005)⁽¹⁰⁴⁾. All of these studies reviewed in this petition support the conclusion that daily consumption of green tea would have a positive impact on reducing a number of risk factors associated with cardiovascular disease (particularly total and LDL-C) and ultimately, on reducing the risk of cardiovascular disease.

13. Additional Issues to Address In Qualified Health Claim Petitions

A. Green tea would provide a meaningful amount of catechins in the diet

At present, the optimal level of green tea or its polyphenol flavonoid catechin intake has not been defined. Neither FDA nor the IOM Expert Panel of the National Academy of Sciences has established a daily value for green tea and its catechins or the flavan-3-ol class of compounds. The current estimated U.S. intake of all teas including green tea on average for individuals age 2 and over was 397 grams or 13.4 ounces (1.6 cups), and at the 95th percentile, it is 31.4 ounces (3.9 cups). Green tea *per se* is not broken out in this consumption data, but clearly, if individual tea consumption shifted slightly to 2-3 cups/day of green tea, it would have a positive and favorable impact on cardiovascular risk factors, which would be highly desirable in reducing the risk of cardiovascular disease without displacing other foods in the diet.

These data support the conclusion that an intake of greater than 1 cup of green tea per day, providing at the minimum 250 mg/day of the catechins present as components of green tea, would have a positive effect on a number of risk factors associated with cardiovascular disease and would either reduce or delay its onset.

The Petitioner recommends that conventional foods meeting the definition to be characterized as green tea be required to contain at least 125 mg of catechins per serving in order to be allowed to bear a qualified health claim for green tea and reduced risk of cardiovascular disease. Consistent with requirements for foods eligible to bear several other health claims, this is based on the desirable green tea intake of 2-3 cups (8 ounce serving/cup) per day, providing a

minimum of 250 mg/day green tea catechins. This would be accomplished with at least two consumption occasions per day.

B. Public Health Benefit

The public health benefit for the general population from the requested qualified health claim for green tea is that it would lead to increased consumption of the flavan-3-ol catechins in green tea, which would be highly desirable for optimal cardiovascular health in reducing both total and LDL-cholesterol, two well recognized risk factors associated with cardiovascular disease. In addition, the recognized antioxidant properties of the catechins in green tea on improving endothelial function by reducing the inflammation process are also supportive of the positive benefits of green tea on cardiovascular health. The recognition by the Agency of the positive and beneficial attributes of green tea and its impact on several of the known risk factors of cardiovascular disease, and allowing this information to be communicated to the public, will provide a valuable educational tool to the consumer in their proactive selection of a food with demonstrated beneficial health attributes.

As a food that has been consumed for centuries, green tea is considered safe for consumption and has not been reported to cause any adverse health effects. As reported in this petition, recent research has demonstrated no adverse effects from the daily consumption of green tea. Chow *et al.* (2003)⁽³⁶⁾ concluded that consumption of green tea catechins, providing the equivalent of EGCG found in 8-16 cups of green tea taken once daily for 4 weeks, was safe. It is also well known that, in Japanese and other Asian populations, it is not at all unusual to consume 10 or more cups of green tea a day with no untoward effects. No adverse effects are anticipated from the consumption of green tea (2-3 cups/day) at the levels proposed in this petition.

We do not expect any substantial changes in dietary eating habits in the U.S. population from an authorized qualified health claim on green tea. Increased RTD green tea intake would be balanced by possible decreases in the intake of other beverages. Further, the use of green tea extracts in dietary supplements would not be expected to affect eating habits. No negative consequences would result in the total diet. The beneficial effect of a reduction and/or delay of the onset in cardiovascular disease is likely to result from consumption of green tea providing approximately 125 mg catechins per serving.

14 Summary and Conclusions

As the preceding review and presentation of the available scientific literature demonstrate, the majority of evidence from publicly available scientific studies supports the association of an increased dietary intake of green tea with reduction in several key risk factors associated with the onset of cardiovascular disease due to green tea's unique polyphenol (flavonoid) content. There is also substantial scientific evidence that establishes the biological plausibility and mechanisms for the protective effect by green tea in this role for the prevention or mitigation of the pathophysiological conditions leading to cardiovascular disease, particularly the significant lowering of total and LDL-cholesterol. The scientific literature clearly demonstrates the beneficial physiological and biochemical effects of the catechin component of green tea as a powerful and protective antioxidant. Evidence supports this role for green tea in the vascular endothelium, where the processes of inflammation, lipid peroxidation and the depositing of fatty streaks in the artery play key roles in the initiation of atherosclerosis. Epidemiological and observational studies in human populations with high intakes of green tea have shown significant reductions in risk factors that are known to be intimately involved in the initiation of cardiovascular disease. Furthermore, the majority of case-control, prospective cohort and intervention studies provide substantial and convincing evidence for reduction in risk of cardiovascular disease from high intakes of green tea.

Clearly, the significant public health benefits of increasing green tea consumption for its beneficial catechins are applicable and would render a significant public health benefit to the U.S. population in an overall reduction in key risk factors associated with the onset of cardiovascular disease. Based on current consumption estimates for total tea (including green tea) that indicate a mean consumption of 1.6 cups/day, a shift to green tea would have no measurable change in the total diet for tea intake and would provide more of the unique flavan-3-ols of the catechin class that are predominantly found in green tea. In this manner, green tea can make a major contribution to overall cardiovascular health as a convenient source of these compounds for consumers.