American Heart Association | American Stroke Association

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September 28, 2012

Office of Nutrition, Labeling and
Dietary Supplements (HFS-800)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
Harvey W. Wiley Federal Building
5100 Paint Branch Parkway
College Park, MD 20740

To whom it may concern:

Enclosed is an original and one copy of a health claim petition entitled, "Petition for the Amendment of the Health Claim Regulation 21 C.F.R. § 101.75 – Dietary Saturated Fat and Cholesterol and Risk of Coronary Heart Disease". This submission is in accordance with 21 C.F.R. § 101.70.

Thank you for your consideration of this petition.

Sincerely,

Rose Marie Robertson MD

Rose Marie Robertson, MD, FAHA, FACC
Chief Science Officer

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DATE:	September 28, 2012
NAME OF PETITIONER:	The American Heart Association
POST OFFICE ADDRESS:	7272 Greenville Avenue Dallas, TX 75231
SUBJECT OF PETITION:	Petition for the Amendment of the Health Claim Regulation 21 C.F.R. § 101.75 – Dietary Saturated Fat and Cholesterol and Risk of Coronary Heart Disease
SUBMITTED TO:	Office of Nutrition, Labeling and Dietary Supplements (HFS-800) Center for Food Safety and Applied Nutrition Food and Drug Administration Harvey W. Wiley Federal Building 5100 Paint Branch Parkway College Park, MD 20740

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Petition for the Amendment of the Health Claim Regulation 21 C.F.R. § 101.75 – Dietary Saturated Fat and Cholesterol and Risk of Coronary Heart Disease

I. INTRODUCTION

The undersigned, the American Heart Association (AHA), submits this petition to amend the dietary saturated fat and cholesterol and risk of coronary heart disease (CHD) health claim regulation (21 C.F.R. § 101.75) to permit raw fruits and vegetables, as well as single-ingredient or mixtures of frozen or canned fruits and vegetables that contain no added fat or sugars (except 100% juice as a packing medium), which fail to comply with the "low-fat" definition (21 C.F.R. § 101.62) and/or the 10% daily value (DV) minimum nutrient content requirement (21 C.F.R § 101.14(e)(6)), to be eligible to bear the claim. Raw fruits and vegetables that would become eligible for this claim include avocados, bamboo shoots, beets, cucumbers, grapes, huckleberries, iceberg lettuce, mushrooms, plums, sea buckthorn berries, scallions and sweet corn. Examples of processed fruits and vegetables that would become so eligible include certain brands of canned cut green beans, French style green beans, sweet corn as well as pears, fruit cocktail and sliced peaches canned in water. Frozen sweet corn would also become eligible. These lists are not exhaustive and it is possible that additional raw or processed fruits and vegetables that would be affected by the proposed amendment will be identified in the future.

The prevention of CHD continues to be a leading public health priority in the U.S. Recent data from the AHA (Roger et al., 2011) shows that 16.3 million Americans have been diagnosed with CHD and 785,000 new cases of this disease are expected each year.

Approximately one in every six deaths in the U.S. during 2007 was attributed to CHD (n=406,351).

Approval of the proposed amendment would allow use of the AHA Heart-Check symbol in labeling of the affected fruits and vegetables. Eligibility for this symbol requires that such products qualify for a CHD-related health claim. The ability to promote fruits and vegetables in this manner has important public health implications because the AHA Heart-Check program has been shown to increase sales of foods with this symbol.

II. PROPOSED REGULATORY ACTION

The current regulatory language for the dietary saturated fat and cholesterol and risk of CHD health claim pertaining to nature of the food (21 C.F.R. § 101.75(c)(2)(ii)) provides,

> (ii) *Nature of the food.* The food shall meet all of the nutrient content requirements of § 101.62 for a "low saturated fat," "low cholesterol," and "low fat" food ….

In addition, 21 C.F.R. § 101.75 (c)(1) provides, "All requirements set forth in § 101.14 shall be met." This requirement includes the 10% DV minimum nutrient content requirement defined in §101.14(e)(6).

AHA recommends the following new subparagraphs be added to replace the sections quoted above to exempt raw fruits and vegetables, as well single-ingredient or mixtures of frozen or canned fruits and vegetables with no added fat or sugars from the "low-fat" and 10% DV minimum nutrient content requirements. Section 101.75(c)(2)(ii) would provide:

> (ii) *Nature of the food.* (A) The food shall meet the nutrient content requirements of § 101.62 for a "low saturated fat" and "low cholesterol" food.
>
> (B) The food shall meet the nutrient content requirements of § 101.62 for a "low fat" food, unless it is a raw fruit or vegetable, or is a single-ingredient or mixture of frozen or canned fruits and vegetables that contains no fats or sugars in addition to the fats or sugars inherently present in the fruit or vegetable product; except that fish and game meats (i.e., deer, bison, rabbit, quail, wild turkey, geese, and ostrich) may meet the requirements for "extra lean" in §101.62.

Additionally, section 101.75 (c)(1) would provide:

> All requirements set forth in § 101.14 shall be met, except 101.14(e)(6) with respect to a raw fruit or vegetable, or to a single-ingredient or mixture of frozen or canned fruits and vegetables.

Raisins and other dried fruits or vegetables (e.g., sun-dried tomatoes) would not be included under the raw fruit and vegetable exemption because AHA believes such foods constitute processed (i.e., dried) forms of the fresh fruit or vegetable (i.e., grapes, tomatoes). Canned vegetables packed in brine would be included in this exemption, but the disqualifier level of 480 mg sodium per reference amount customarily consumed (21 C.F.R. § 101.14(a)(4)) would apply.

As discussed later in this document, regulatory precedence may give more credence to the proposed exemption for raw fruits and vegetables than that for their canned and frozen counterparts. AHA believes, and the Dietary Guidelines for Americans recommends, that all fruits and vegetables, whether raw or processed, can make valuable contributions to a heart-healthy eating pattern. However, in the interest of public health, we urge the agency to move forward with the raw fruit and vegetable exemption alone should the exemption for canned and frozen fruits and vegetables, as proposed in this document, require additional consideration.

AHA also believes that the scientific evidence supports the exemption of all foods that otherwise qualify for the dietary saturated fat and cholesterol and risk of CHD health claim from the "low-fat" requirement for this claim (in addition to the raw and processed fruits and vegetables enumerated above). For example, FDA has already granted qualified health claims (QHCs) for select tree nuts, olive, canola and corn oils as well as moderate fat whole-grain products. We, therefore, would not object if the Food and Drug Administration (FDA) provided such a broad exemption. However, the current petition applies solely to fruits and vegetables (foods clearly shown to have cardioprotective properties according to the scientific evidence discussed below) and the agency may wish to consider additional exemptions to this requirement for other foods or food groups on a case-by-case basis if subsequent petitions are submitted.

Finally, the AHA strongly believes the evidence presented in this petition is so compelling, and the potential to encourage increased consumption of fruits and vegetables so important from a public health perspective, that we respectfully request that FDA issue an interim final rule authorizing the proposed amendment.[1] This action will

[1] FDA may proceed with amendment of the health claim regulation as an interim final rule to enable consumers to develop and maintain healthy dietary practices and/or to ensure that scientifically sound nutritional and health information is provided to consumers as soon as possible. 21 U.S.C. § 343(r)(7)(A). The agency has employed this rulemaking authority in promulgating/amending 21 C.F.R. §§ 101.83 to

allow use of the claim and the AHA Heart-Check symbol on affected foods as expeditiously as possible.

III. SCIENTIFIC BASIS

A. Introduction

AHA strongly believes that fruits and vegetables, as a group, should qualify for the dietary saturated fat and cholesterol and risk of CHD health claim based on scientific evidence that they contribute to reduced risk of CHD regardless of their naturally-occurring fat content or status regarding the 10% DV minimum nutrient contribution requirement for health claims. A comprehensive review of the observational studies that examined the association of fruits and vegetables, as a group, on CHD or its biomarkers, as well as a review of the intervention studies that examined such an effect for individual raw fruits and vegetables that would become eligible for the claim under the proposed amendment is provided below. In addition, a brief summary of the benefits of fruits and vegetables that extend beyond CHD, as well as the scientific developments that led to the current understanding that total fat is unrelated to risk of CHD, will be presented.

B. General benefits of fruits and vegetables

Fruits and vegetables are among the most highly recommended foods by governmental and non-governmental public health organizations. For example, the 2010 *Dietary*

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authorize health claims on the association between plant sterol/stanol esters and reduced risk of CHD (65 Fed. Reg. 54,685 (Sept. 8, 200)); 101.81to add barley betafiber as an additional eligible source of beta-glucan soluble fiber (73 Fed. Reg. 9938 (Feb. 25, 2008)), to add barley as an additional eligible source of beta-glucan soluble fiber (70 Fed. Reg. 76,150 (Dec. 23, 2005)), and to add oatrim as an additional eligible source of beta-glucan soluble fiber (67 Fed. Reg. 61,773 (Oct. 2, 2002)); and 101.80 to include isomaltulose, a noncariogenic sugar (72 Fed. Reg. 52,783 (Sept. 17, 2007)) and to include the sugar D-tagatose as eligible for the health claim (67 Fed. Reg. 71,461 (Dec. 2, 2002)). Proceeding with amendment of 21 C.F.R. § 101.75 as an interim final rule would be consistent with these precedents.

Guidelines for Americans (*DGA*) (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2010) recommend increased consumption of these food groups in the areas of "weight management", "foods and nutrients to encourage" and "healthy eating patterns." The *DGA* specifically noted that increased consumption of fruits and vegetables may reduce the risk of certain cancers, as well as CHD and other forms of cardiovascular disease (CVD).

Fruits and vegetables also have many desirable nutritional characteristics. These foods have higher nutrient-density scores (nutrients/1,000 kcal) than any other food group due to their high nutrient content and low energy density (kcal/100 g) (Darmon et al., 2005). The *DGA* (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2010) noted that most vegetables and fruits are major contributors of nutrients that are under-consumed in the U.S. including folate, magnesium, potassium, dietary fiber and vitamins A, C and K. USDA data[2] show that fruits and vegetables are rich sources of flavonoids including the flavonols (e.g., spinach, tomatoes, broccoli, apples, onions, cranberries), flavones (e.g., spinach, parsley), flavones (oranges), flavon-3-ols (e.g., apricots, peaches) and anthocyanidins (strawberries, blueberries) (Most, 2004). In addition, it has long been recognized that frequent consumption of fruits and vegetables is associated with a healthy dietary pattern (Osler and Heitmann, 1997, Randall et al., 1991).

[2] USDA Database for the Flavonoid Content of Selected Foods, Release 3 (2011) http://www.ars.usda.gov/services/docs.htm?docid=6231

C. Benefits of fruits and vegetables other than CHD

1. Non-cardiovascular conditions

Considerable research has been conducted to examine the potential health benefits of fruits and vegetables. In addition to their cardioprotective properties (which will be discussed below), considerable scientific evidence suggests that these food groups have benefits in the areas of weight management (Davis et al., 2006, Bes-Rastrollo et al., 2008, Vernarelli et al., 2011, Rolls et al., 2004, DellaValle et al., 2005, Ledoux et al., Alinia et al., 2009), type-2 diabetes (Salas-Salvado et al., 2011), metabolic syndrome (Kim and Jo, 2011, Abete et al., 2011) and certain cancers, including colorectal (Aune et al., 2011), lung (Lam et al., 2009), oral cavity (Pavia et al., 2006), pancreas (Bae et al., 2009), stomach (Bae et al., 2008) and possibly endometrium (Bandera et al., 2007), but not breast (Smith-Warner et al., 2001).

2. Stroke

Considerable evidence also exists that shows fruits and vegetables are beneficially associated with the incidence of stroke. This condition is not included in the health claim AHA is proposing to amend, but the observation of such a protective association lends credence to the cardiovascular benefits of fruits and vegetables beyond CHD, and further illustrates the benefits of encouraging their consumption through use of the claim and the AHA Heart-Check symbol. These studies are discussed briefly below in chronological order by year of publication.

Gillman et al. (1995) reported that each increase of three servings of fruits and vegetables per day was associated with a reduced risk of stroke (RR (relative risk) = 0.74; 95% CI (confidence interval), 0.56-0.96) among 832 healthy men followed for an average of 20 years in the Framingham Study. Ischemic stroke (RR=0.76; 95% CI, 0.57-1.02) and hemorrhagic stroke (RR=0.49; 95% CI, 0.25-0.95) were also inversely associated with fruit and vegetable intake.

One of only two prospective cohort studies identified that did not report a protective association for stroke was a small study by Keli et al. (1996). A cohort of 552 men was followed for an average of 15 years. During this time there were 42 cases of non-fatal first stroke. The risk of this malady was directionally protective for total fruit consumption (RR=0.52; 95% CI, 0.21-1.31) and total vegetable consumption (RR=0.82; 95% CI, 0.35-1.94), but these associations were not statistically significant. The relatively wide 95% CI ranges due to small sample size may have been responsible for the lack of significant findings.

Joshipura et al. (1999) observed a protective association between fruit and vegetable intake and ischemic stroke among more than 75,000 women in the Nurses' Health Study after eight years of follow-up. Each serving of fruits or vegetables reduced risk of this condition by 6% (RR=0.94; 95% CI, 0.90-0.99). Similar associations were observed for each additional serving of cruciferous vegetables (RR=0.68; 95% CI, 0.49-0.94) and green leafy vegetables (RR=0.79; 95% CI, 0.62-0.99). There were also protective associations for citrus fruits, including juice and citrus fruit juice.

Hirvonen et al. (2000) reported that vegetable consumption was inversely associated with cerebral infarction (RR=0.71; 95% CI, 0.57-0.87) and fruit consumption was inversely associated with hemorrhagic stroke (RR=0.43; 95% CI, 0.22-0.81) among 26,593 male smokers without a history of stroke over an average follow-up period of 6.1 years. There were non-significant inverse associations between vegetable intake and hemorrhagic stroke as well as between fruit consumption and ischemic stroke.

Bazzano et al. (2002) observed that stroke incidence was inversely associated with frequency of fruit and vegetable intake (RR=0.73; 95% CI, 0.57-0.95) among 9,608 participants in the first National Health and Nutrition Examination Survey (NHANES) survey followed for 19 years. There was also a trend ($p<0.05$) for such an association with stroke mortality (RR=0.58; 95% CI, 0.33-1.02).

Sauvaget et al. (2003) found that total stroke was inversely associated with green-yellow vegetable intake (RR=0.77; 95% CI, 0.62-0.95 in men and RR=0.81; 95% CI, 0.68-0.96 in women) as well as total fruit consumption (RR=0.65; 95% CI, 0.53-0.80 in men and RR=0.75; 95% CI, 0.64-0.88 in women) among a Japanese cohort (n=40,349) followed for 18 years. Protective associations for both hemorrhagic and ischemic stroke for both of these dietary components were also reported.

The other prospective cohort study that did not report a protective association between fruit and/or vegetable intake and stroke was Steffen et al. (2003). Multivariate analysis showed that ischemic stroke incidence was not associated with intake of these foods

(RR=0.94; 95% CI, 0.54-1.63) among 15,792 members of the Atherosclerosis Risk in Communities (ARIC) cohort after 11 years. Fruit and vegetable intake were protective for all-cause mortality (RR=0.53; 95% CI, 0.42-0.68) after adjustment for age, race, gender and time-dependent energy intake, and there was a trend for such an association (RR=0.78; 95% CI, 0.61-1.01; p for trend = 0.02) when adjusted for a wider range of potentially confounding variables.

Johnsen et al. (2003) reported that intake of all fruit was inversely associated with ischemic stroke (RR=0.60; 95% CI, 0.38-0.95) after adjustment for a wide range of potentially confounding variables among 54,506 men and women in the Danish Diet, Cancer, and Health Study after a mean follow-up period of 3.09 years. Total fruit and vegetable intake was also associated with this parameter (RR=0.63; 95% CI, 0.41-0.96) after adjustment for sex, total energy intake and smoking status, but not after further adjustment for blood pressure, serum total cholesterol (T-C), body mass index (BMI), history of diabetes, alcohol, red meat and omega-3 fatty acid intake as well as physical activity and education (RR=0.72; 95% CI, 0.47-1.12). There was also an association between all vegetables and stroke (RR=0.63; 95% CI, 0.43-0.92) on an unadjusted basis, but not after correcting for the potentially confounding variables noted above.

Finally, a small case-control study from France (Mahe et al., 2010) reported greater (p=0.004) consumption of fruits and vegetables among 50 healthy control subjects than among 24 ischemic stroke patients less than 65 years of age.

The consistent protective associations reported by these epidemiological studies are reflected in two meta-analyses of the prospective cohort studies. Dauchet et al. (2005) examined seven such studies that included 141,536 women and 90,513 men. The combined incidence of stroke was 2,955. Each additional portion of fruit and vegetable decreased risk of stroke by five percent (RR=0.95; 95% CI, 0.92-0.97), each portion of fruit by 11% (RR=0.89; 95% CI, 0.85-0.93) and there was a trend for such an association for vegetables (RR=0.97; 95% CI, 0.92-1.02). The authors concluded, "This meta-analysis of cohort studies suggests that fruit and fruit and vegetable consumption decreases the risk of stroke."

Similarly, a meta-analysis conducted by He et al. (2006) among eight studies (n=257,551, stroke incidence = 4,917) with an average follow-up period of 13 years reported that consumption of three servings of fruits and vegetables per day was associated with an 11% reduction in risk of stroke (RR=0.89; 95% CI, 0.83-0.97) while that of three to five servings or more was associated with a 26% reduction in risk (RR=0.74; 95% CI, 0.69-0.79). The authors concluded, "Our results provide strong support for the recommendations to consume more than five servings of fruit and vegetables per day, which is likely to cause a major reduction in strokes."

D. Fruits and vegetables and risk of CHD

1. Observational studies on fruits and/or vegetables and CHD related risk factors

The majority of prospective cohort and other observational studies reported protective associations between fruit and/or vegetables and incidence of CHD and/or one of its major risk factors (e.g., blood pressure). The studies that were identified are briefly discussed below in chronological order by year of publication.

Knekt et al. (1996) reported that fruits other than those high in flavonoids (i.e., apples and berries) were inversely associated with death due to CHD among 2,385 Finnish women (RR=0.55; 95% CI, 0.34-0.90) with a trend for such an association among 2,748 men (RR=0.88; 95% CI, 0.65-1.20) after adjustment for age, smoking, serum T-C, hypertension and BMI. The subjects were 30-69 years of age at baseline and were followed for 20-25 years. There was also an inverse association between consumption of such fruits with total mortality for women (RR=0.70; 95% CI, 0.54-0.91) and men (RR=0.77; 95% CI, 0.64-0.93). Total vegetable consumption was not associated with CHD incidence among women (RR=0.77; 95% CI, 0.49-1.21) or men (RR=0.89; 95% CI, 0.65-1.21). Consumption of apples (RR=0.57; 95% CI, 0.36-0.91) and berries (RR=0.59: 95% CI, 0.36-0.94) were also inversely associated with CHD among women, but not in men. The authors concluded that people with very low intakes of flavonoids have higher risk of CHD.

Mann et al. (1997) conducted a prospective cohort study among 10,802 health conscious women and men between 16 and 79 years of age at baseline living in the U.K with a mean follow-up period of 13.3 years. There were no associations between intake of green vegetables or carrots (RR=1.34; 95% CI, 0.47-3.84 and RR=0.76; 95% CI, 0.37-1.57, respectively) and death due to ischemic heart disease (IHD). There were also no significant associations between IHD death and intake of nuts, dietary fiber, alcohol, fish or vegetarianism. Total fat, saturated fat and dietary cholesterol yielded positive associations. The data were corrected for age, sex, smoking and social class. The authors speculated that the lack of protective associations for healthy dietary practices was due to the high health status of the population. The subjects were generally non-smokers, (83.7% of women and 75.3% of men), lean (89.6% of women and 83.2% of men had BMI values <25) and of high social class. The subjects also consumed diets that were low in saturated fat, cholesterol, total fat and relatively high in dietary fiber. The authors also noted that the food frequency questionnaire used for the study was validated for dietary fiber, but not for other nutrients. A final limitation of the study was the fact that only 64 deaths due to IHD were observed during the follow-up period.

Liu et al. (2000) studied the association between fruit and vegetable intake and risk of cardiovascular disease (CVD) among 39,876 participants in the Women's Health Study followed for an average of five years. Among all participants, intake of fruits and vegetables, as a group, was inversely associated with incidence of myocardial infarction (MI) (RR=0.47; 95% CI, 0.28-0.79) after correction for age and treatment, but the association was attenuated after multivariate adjustment (RR=0.63; 95% CI, 0.38-1.17).

A similar situation occurred for intake of all fruits as a group (RR=0.40; 95% CI, 0.24-0.68 and RR=0.66; 95% CI, 0.36-1.22 for the age/treatment adjusted and multivariate adjusted associations, respectively). There were no significant associations between the consumption of all vegetables and incidence of MI in this group. However, the investigators noted that incidence of CVD has the potential to alter dietary consumption and therefore confound results from prospective studies. Therefore, subjects with self-reported diabetes, history of hypertension or high cholesterol at baseline were excluded. This approach resulted in protective associations for incidence of MI with multivariate-corrected consumption of all fruits and vegetables (RR=0.45; 95% CI, 0.22-0.91) and of all vegetables as a group (RR=0.45; 95% CI, 0.24-0.89). There was also a protective association for consumption of all fruit in this sample (RR=0.43; 95% CI, 0.24-0.78) after age/treatment correction, but multivariate adjustment attenuated the association (RR=0.57; 95% CI, 0.30-1.09). The authors concluded, "These data suggest that higher intake of fruit and vegetables may be protective against CVD and support current dietary guidelines to increase fruit and vegetable intake."

Liu et al. (2001) reported data on the association of vegetables high in carotenoids among 15,071 members of the Physicians' Health Study who were free of CVD and cancer at baseline. There was an inverse association between the number of vegetable servings per day and total CHD (defined as MI, coronary artery bypass and/or coronary angioplasty) (RR=0.77; 95% CI, 0.60-0.98) during a 12 year follow-up period. Further analysis revealed that CHD risk would be reduced by 17% (RR=0.83; 95% CI, 0.71-0.98) for each additional serving of vegetables consumed. The multivariate-adjusted association for MI *per se* was not statistically significant (RR=0.81; 95% CI, 0.59-1.31). It was noted that inverse associations were observed for CHD with all individual types of vegetables examined (i.e., cruciferous, dark yellow, green leafy and tomatoes); however, the specific data were not published. The authors concluded, "Our results suggest an inverse association between vegetable intake and risk of CHD. These prospective data support current dietary guidelines to increase vegetable intake for the prevention of CHD."

Hirvonen et al. (2001) examined the associations between fruit and vegetable intake and MI incidence and death among 25,372 Finnish male smokers, 50-69 years of age at baseline with no prior MI who were participants in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. The participants were followed for an average of 6.1 years. Vegetable consumption (measured as grams per day) was inversely associated with nonfatal MI (RR=0.77; 95% CI, 0.63-0.94) and fatal MI (RR=0.68; 95% CI, 0.50-0.95) after adjustment for a wide range of potentially confounding variables. The associations for total fruit consumption and nonfatal and fatal MI were also inverse, but did not reach statistical significance (RR=0.87; 95% CI, 0.72-1.05 and RR=0.87; 95% CI, 0.70-1.08, respectively). The study was designed to examine intake of flavonols and flavones and did not specifically identify the fruits and vegetables included in the analysis.

Joshipura et al. (2001) studied 84,251 women (34-59 years of age at baseline) and 42,148 men (40-75 years) who were free of CVD, diabetes and cancer at baseline. The women were members of the Nurses' Health Study cohort and were followed for 14 years. The men were members of the Health Professionals' Follow-Up Study and were studied for eight years. Statistically significant multivariate-adjusted inverse associations with CHD were reported for all vegetables and fruits as a group (RR=0.80; 95% CI, 0.69-0.93), all fruits (RR=0.87; 95% CI, 0.69-0.92) and all vegetables (RR=0.82; 95% CI, 0.71-0.94). An increase of one serving per day of these categories was predicted to reduce CHD incidence by 4% for total fruits and vegetables (RR=0.96; 95% CI, 0.94-0.99), by 6% for all fruits (RR=0.94; 95% CI, 0.90-0.98) and by 5% (RR=0.95; 95% CI, 0.92-0.99) for total vegetables. There were also inverse associations for total citrus fruit (RR=0.88; 95% CI, 0.77-1.00), cruciferous vegetables (RR=0.86; 95% CI, 0.75-0.99), and green leafy vegetables (RR=0.72; 95% CI, 0.63-0.83), but not for vitamin C-rich fruits and vegetables (RR=0.91; 95% CI, 0.70-1.04) or potatoes (RR=1.15; 95% CI, 0.78-1.70). Despite non-significant associations that compared the highest and lowest quintiles, an increase of one serving per day of vitamin C-rich fruit was inversely associated with risk of CHD (RR=0.94; 95% CI, 0.88-0.99). The authors concluded, "Consumption of fruits and vegetables, particularly green leafy vegetables and vitamin C-rich fruits and vegetables, appears to have a protective effect against coronary heart disease."

Bazzano et al. (2002) examined 9,608 adults (25-74 years of age at baseline) who were participants in the first NHANES for an average follow-up period of 19 years. Consumption of three or more servings of fruits and vegetables per day was inversely associated with age, race, gender and energy intake-adjusted risk of IHD mortality compared to consumption of less than one serving per day (RR=0.66; 95% CI, 0.49-0.90) and a trend for such an association after multivariate adjustment (RR=0.76; 95% CI, 0.56-1.03; p for trend = 0.07). There was a similar trend for age, race, gender and energy intake-adjusted risk of IHD incidence (RR=0.85; 95% CI, 0.72-1.02; p for trend = 0.02), but not after multivariate adjustment (RR=1.01; 95% CI, 0.84-1.21). Subgroup analysis showed that fruit and vegetable consumption was significantly associated with reduced risk of IHD mortality among white participants (RR= 0.68; 95% CI, 0.48-0.97), but not among non-white participants (RR=1.19; 95% CI, 0.66-2.14). The interpretation of this study is limited by the fact that NHANES dietary data are obtained by 24-hour recall and may not reflect typical dietary intakes which are better obtained by food frequency questionnaires. Nevertheless, the investigators concluded, "Nutrients in whole foods, such as fruits and vegetables, may have additive and synergistic effects not available through dietary supplementation. In addition, this study provides additional evidence for recommendations to increase fruit and vegetable intakes as part of a dietary approach to prevent cardiovascular disease."

Steffen et al. (2003) examined the association of fruit and vegetables (also whole and refined grains) with incidence of coronary artery disease (CAD) among 15,792 participants (45-64 years of age at baseline) free of CAD upon enrolment in the Atherosclerosis Risk in Communities Study during an 11-year follow-up period. CAD incidence was inversely associated with intake of fruit and vegetables (RR=0.56; 95% CI, 0.42-0.81) after adjustment for age, race, gender and energy intake, but not after further adjustment for a wide variety of CVD risk factors (RR=0.82; 95% CI, 0.57-1.17). There was a trend for such a fully adjusted association for all-cause mortality (RR=0.78; 95% CI, 0.61-1.01; p for trend = 0.02). The authors concluded, "These observational findings suggest a beneficial effect of whole-grain and fruit and vegetable consumption on the risks of total mortality and incident CAD, but not on the risk of ischemic stroke."

Yusuf et al. (2004) conducted a large case-control study among 15,152 acute MI patients and 14,820 age and gender-matched apparently healthy controls from 262 centers in 52 countries. Daily consumption of vegetables and fruit compared to lack of daily consumption of these foods was inversely correlated with MI (RR=0.70; 95% CI, 0.64-0.77) after adjustment for age, gender and smoking. This association remained essentially unchanged after adjustment for numerous other potentially confounding variables (RR=0.70; 95% CI, 0.62-0.79). This study is limited by the categories used to classify fruit and vegetable consumption (i.e., virtually no consumption to minimal consumption of one fruit and vegetable per day). The study would have been more informative had consumption of these foods been divided into more narrow categories. The case-control nature of the study also limits the conclusions that can be drawn because of inherent limitations to this design (i.e., cases may have altered their diets as a result of the condition). Nevertheless, the study provides support for the cardioprotective properties of fruits and vegetables.

Ness et al. (2005) studied the association between childhood intake of vegetables and CHD mortality in a small cohort (n=4,028) of children living in the U.K. who were surveyed between 1937 and 1939. The mean follow-up period was 37 years. Food consumption was not measured directly, but was assessed by an inventory of foods brought into the home. There was a trend for an inverse association (p=0.07) between fruit and vegetable "intake" and CHD after adjustment for age, energy, gender, childhood family food expenditure, father's social class, district of residence as a child, period of birth, season when studied as a child, and Townsend score for current address or place of death. The RR's were only presented graphically, but visual inspection suggests a value of approximately 0.58 with a 95% CI of ~0.3-1.05. This study must be interpreted with caution due to the lack of dietary data and other information. Nevertheless, it provides suggestive support for the cardioprotective properties of fruit and vegetables as a group.

Tucker et al. (2005) reported an analysis of data from the Baltimore Longitudinal Study of Aging. This small cohort was composed of 501 men born before 1929 who had no history of angina pectoris or MI at baseline. There were 71 deaths during a mean follow-up period of 18 years. Fruit and vegetables (servings per day) were associated with reduced risk of CHD mortality (RR=0.84; 95% CI, 0.72-0.99) after adjustment for age at first visit, energy intake, BMI, smoking, alcohol use, physical activity score, supplement use and saturated fat intake. Vegetable consumption was also inversely associated with CHD death after controlling for these variables (RR=0.65; 95% CI, 0.50-0.85); however, fruit consumption alone was not (RR=0.97; 95% CI, 0.78-1.20). Further control for secular trend (year of first visit before versus after 1980) attenuated the association for fruit and vegetable servings combined (RR=0.90; 95% CI, 0.76-1.05), but not for vegetables alone (RR=0.73; 95% CI, 0.54-0.97). The data also showed that consumption of greater than or equal to five servings fruits and vegetables per day in conjunction with greater than 12% of energy (en) saturated fat was inversely associated (after full adjustment) with CHD mortality (RR=0.46; 95% CI, 0.21-0.99), as was consumption of fewer than five servings of fruits and vegetables in conjunction with a low saturated fat intake (≤12% en) (RR=0.41; 95% CI, 0.17-0.98). However, the combination of high fruits and vegetables and low saturated fat resulted in the highest level of risk reduction (RR=0.37; 95% CI, 0.16-0.81). The authors suggested that the mechanism of cardioprotection for fruits and vegetable is different from that of low saturated fat because the combination of the two factors was more protective than either alone.

Dauchet et al. (2007) studied the association between diet and changes in blood pressure (BP) among 4,652 French adults (35-63 at baseline) during a mean follow-up period of 5.4 years. Cross-sectional analysis of baseline data (n=4,652) showed that upper tertile consumption of fruits and vegetables (646 g/d) was associated with a 1.4 mm Hg lower systolic blood pressure (95% CI, -2.6 to -0.2) after adjustment for potentially confounding variables as well as a 0.9 mm Hg lower diastolic blood pressure (95% CI, -0.9 to -0.2). Similar results were observed for the Dietary Approaches to Stop Hypertension (DASH) diet score. Longitudinal analysis (n=2,341) yielded similar results for systolic blood pressure (-2.1 mm Hg; 95% CI, -3.6 to -0.7) and a trend for such an association for diastolic blood pressure (-0.8; 95% CI, -1.7 to 0.2; p for trend <0.04). Once again, a similar pattern was observed for the DASH diet score. The authors concluded, "These results suggest that high fruit and vegetable intakes may be associated with a lower increase in BP with aging."

Lanas et al. (2007) conducted a case-control study among 1,237 first acute MI patients and 1,888 age, gender and center-matched controls living in Argentina, Brazil, Colombia, Chile, Guatemala or Mexico who were participants in the INTERHEART Study. Daily consumption of fruits and/or vegetables was inversely associated with MI (RR=0.63; 95% CI, 0.51-0.78) in these countries. Data from subjects in the INTERHEART Study who resided outside of the Latin American countries noted above also indicated a protective association with MI (RR=0.78; 95% CI, 0.73-0.84).

A prospective study of 77,891 women and men (45-74 years of age at baseline) living in Japan was reported by Takachi et al. (2008). Mean follow-up period was approximately 5.5 years. Fruit and vegetable consumption was inversely associated with CVD (RR=0.76; 95% CI, 0.65-0.90) after adjustment for age, gender and study center, but the association was attenuated when adjusted for numerous other potentially confounding variables (RR=0.90; 95% CI, 0.75-1.07). However, fully adjusted inverse associations were observed for total fruit consumption (RR=0.81; 95% CI, 0.67-0.97) and citrus fruit consumption (RR=0.80; 95% CI, 0.67-0.95), but not total vegetable intake (RR=0.97; 95% CI, 0.81-1.15). It is possible that the high consumption of vegetables among the Japanese population contributed to the lack of an association due to the possibility that typical consumption is beyond a threshold level for a protective effect of such foods.

The most recent observational study in this area that was identified was a prospective assessment of the association between fruit and vegetable intake and IHD mortality from the European Prospective Investigation into Cancer and Nutrition (EPIC) Heart Study (Crowe et al., 2011). The cohort consisted of 313,074 women and men who were free of MI or stroke at baseline living in eight European countries who were followed for an average period of 8.4 years. Combined consumption of fruits and vegetables was inversely associated (RR=0.78; 95% CI, 0.65-0.95) with IHD mortality after adjustment for gender, study center, smoking, alcohol intake, BMI, physical activity, marital status, education level, employment status, hypertension, angina pectoris, diabetes mellitus and total energy intake. In addition, total fruit intake (RR=0.80; 95% CI, 0.69-0.94), but not total vegetable intake (RR=0.93; 95% CI, 0.77-1.12) was significantly associated with death from IHD. The association for total fruit and vegetable intake (RR=0.95; 95% CI, 0.91-0.99, p for trend =0.033) and fruit intake (RR=0.95; 95% CI, 0.91-1.00, p for trend = 0.047) remained significant after further adjustment for cereal fiber and saturated fat intake. After calibration of fruit and vegetable intake to account for differences in dietary assessment between the participating centers, a one portion (80 g) increment in fruit and vegetable intake was associated with a 4% lower risk of fatal IHD (RR = 0.96; 95% CI, 0.92–1.00, p for trend =0.033). The authors concluded that higher intake of fruits and vegetables are associated with a reduced risk of IHD mortality, but noted uncertainty about the causality and mechanism of such effects.

Three meta-analyses have been published that examined the pooled data from prospective cohort studies. An early meta-analysis by Law and Morris (1998) pooled data from three studies that examined the association between total fruit consumption and IHD incidence, as well as two studies that examined such a relationship for total vegetable consumption. The authors concluded there was about a 15% lower risk of this malady at the 90^{th} than 10^{th} centile of fruit and vegetable consumption; however, the 95% CIs included unity

(RR=0.86; 95% CI, 0.71-1.05 for all fruits and RR=0.82; 95% CI, 0.66-1.02 for all vegetables).

A more recent meta-analysis (Dauchet et al., 2006) was based on nine prospective cohort studies (all of which were discussed above). The analysis included 129,701 women and 91,379 men from nine studies that observed 5,007 CHD events. The risk of CHD was reduced by 4% (RR=0.96; 95% CI, 0.93-0.99, p for trend = 0.0027) for each additional daily serving of fruit and vegetable combined. There were also significant protective associations for CHD risk for fruits as a group (RR=0.93; 95% CI, 0.89-0.96) and vegetables as a group (RR=0.74; 95% CI, 0.75-0.84). The authors concluded that fruit and vegetable consumption is inversely related to risk of CHD.

The most recent meta-analysis of prospective cohort studies in this area was reported by He et al. (2007). The analysis included 12 studies consisting of 13 independent cohorts (all of which were discussed above) with a population of 274,459 subjects and 9,143 CHD events. The mean follow-up period was 11 years. Compared with subjects who consumed less than three servings of fruits and vegetables per day, the pooled RR for those with three to five servings was 0.93 (95% CI, 0.86-1.00, p for trend = 0.06), while that for participants who consumed more than five servings per day was stronger at 0.83 (95% CI, 0.77-0.89; p for trend <0.0001). The protective associations for more than five servings per day were also impressive for fruits as a group (RR=0.87; 95% CI, 0.80-0.95) and for vegetables as a group (RR=0.84; 95% CI, 0.76-0.92). The authors concluded, "These results provide strong support for the recommendations to consume more than five servings per day of fruit and vegetables."

2. Intervention studies on CHD biomarkers for fruits and/or vegetables as a group[3]

The majority of controlled dietary intervention studies reported that fruit and/or vegetable intake beneficially affected one or more of the major CHD-related risk factors (e.g., blood pressure, blood lipid concentrations). The studies that were identified are briefly discussed below in chronological order by year of publication.

Grande et al. (1974) examined the effect of supplementing the diet of 12 young men with 500 kcal of carbohydrate from sucrose, wheat flour, mixed fruits or mixed vegetables using a randomized, cross-over protocol with two-week intervention periods. The subjects consumed a "controlled house diet" during a 17-day run-in period, as well as 10 day wash-out periods between treatments. The diets were similar in protein, fat and total carbohydrate content. The fruit supplement contained a mixture of apple, apricot, banana, date, fig, grape, grapefruit, orange, peach, pear, pineapple, prune, raisin, strawberry and tomato. The vegetable supplement consisted of a mixture of cucumber, green pepper, pumpkin, water chestnut, broccoli, Brussels sprouts, cabbage, celery, cauliflower, lettuce, beet, carrot, green onion, parsnip, rutabaga, sweet potato and turnip. Fasting mean T-C concentrations were lower ($p<0.01$) after the vegetable treatment (172

[3] Two studies by Singh et al. (1992a, 1992b) reported that an intervention that included fruits and vegetables had positive effects on cardiovascular risk factors among Indian CHD patients. However, these studies have been widely criticized in the literature because of substantial concerns related to the accuracy of their results and are therefore not discussed in this section.

mg/dl) than after the other treatments (sucrose = 194, wheat flour = 187, fruits = 192, mg/dl). There were no differences in serum triglyceride (TG) concentrations.

Fraser et al. (1981) examined the effect of three types of vegetables on serum lipids compared to sucrose among 16 healthy male students. Vegetables or sucrose were provided using a Latin square design for intervention periods of three weeks. The paper did not specify whether wash-out periods were employed. The diets were isocaloric and similar in macronutrient content. The supplements consisted of 400 kcal sucrose, 200 kcal leafy vegetables plus 200 kcal sucrose, 300 kcal root vegetables plus 100 kcal sucrose, and 400 kcal whole grains. The leafy vegetable supplement contained a mixture of cabbage, broccoli, Brussels sprouts, celery, lettuce, onions, cauliflower and spinach. The root vegetable supplement consisted of sweet potatoes, parsnips, carrots, beets, rutabagas and turnips. The whole grain supplement was a mixture of wheat (shredded), corn (meal with germ or popcorn) and oat (as oatmeal). T-C concentrations were lower ($p<0.01$) after the leafy vegetable diet and the whole grain diet compared to the sucrose treatment. Low-density lipoprotein cholesterol (LDL-C) concentrations were lower after whole grain diet ($p<0.01$) and trended lower after the leafy vegetable diet ($p<0.10$) compared to the sucrose treatment. Very low-density lipoprotein cholesterol (VLDL-C) 箕 数 箋 紆 絲 聋 聘 胆 胎 胧 胜 □□□□□劄□the leafy vegetable diet than the were no differences between the root vegetable treatment and the sucrose diet. The authors concluded, “In summary, this study shows that vegetables as usually eaten are associated with lower levels of serum total cholesterol as compared to eating sucrose.

This result is not confined to one anatomical vegetable grouping or one lipoprotein fraction."

A study designed to examine the effect of increasing daily fruit and vegetable consumption for eight weeks on circulating lipid and antioxidant concentrations among 98 healthy volunteers living in the U.K. was reported by Zino et al. (1997). Baseline consumption of fruits and vegetables was 2.2 servings per day. Consumption remained constant after the intervention in the control group (2.4 servings/day), but increased to 7.1 servings per day in the experimental group. The intervention resulted in significant ($p<0.05$) increases in dietary energy (263 kcal/d), carbohydrate (4.3 % en), fiber (6.2 g/d) and decreases in saturated fatty acids (-1.7 % en from 17 to 15) and monounsaturated fatty acids (MUFA) (-1.5 % en, from 12 to 11% en). The intervention resulted in increases ($p<0.05$) in plasma ß-carotene, α-carotene and vitamin C, but not α-tocopherol or retinol. There were no changes in plasma T-C, LDL-C, HDL-C or TG. The lack of change in plasma lipids may have been due to the fact that the subjects were normocholesterolemic at baseline (mean plasma T-C = 194 mg/dL), and the fact that the reduction in saturated fatty acid intake that accompanied the intervention was relatively small. Nevertheless, this lack of response was accompanied by significant increases in intake and plasma concentrations of vitamin C and the vitamin A precursors ß- and α-carotene, which suggests adequate dietary compliance. This observation illustrates that compliance with the 10% DV minimum nutrient content requirement does not ensure a beneficial effect on circulating lipids.

Seven studies with the DASH diet that reported changes in blood pressure or other CHD risk factors that also examined a diet high in fruits and vegetables (similar to the DASH diet, but without its low-fat dairy component) were published beginning in 1997 (Appel et al., 1997, Chen et al., 2010, Conlin et al., 2000, Moore et al., 2001, Obarzanek et al., 2001, Sacks et al., 2001, Svetkey et al., 1999). The initial trial (Appel et al., 1997) reported the effect of a diet rich in fruits and vegetables, as well as that of the DASH diet, on blood pressure compared to a the control diet. The control diet was typical of the average U.S. diet and contained 3.6 servings of fruits and vegetables per day. The fruit and vegetable diet was similar to the control diet except that the servings of fruits and vegetables were increased to 8.5 servings per day. Fresh, canned, frozen and dried forms of fruits and vegetables were utilized. The macronutrient content of the diets appeared to be similar, but statistical analysis was not provided. Dietary fiber content was not available, but the potassium content of the fruit and vegetable diet was considerably higher than that of the control diet (4,101 vs. 1,752 mg/d). The subjects were 459 adults with systolic blood pressures less than 160 mm Hg and diastolic blood pressures in the range of 80-95 mm Hg. All subjects consumed the control diet during a 3-week run-in period and were then randomized to one of the three diets for eight weeks. The fruit and vegetable group experienced a significant reduction in systolic blood pressure (-2.8 mm Hg, $p<0.001$) compared to the control group. There was also a trend toward lower diastolic blood pressure between these two groups (-1.1 mm Hg, $p=0.07$). These results were not as dramatic as the blood pressure reductions caused by the DASH diet compared to the control (-5.5 mm Hg systolic and -3.0 mm Hg diastolic, both $p<0.001$), but they provide strong evidence that fruits and vegetables, as a group, lowered blood pressure among non-hypertensive adults. These results were also summarized in a subsequent publication (Sacks et al., 1999). Subgroup analysis of pre-hypertensive subjects (systolic and diastolic blood pressure 140-159 and 90-95, respectively) from the DASH trial (Conlin et al., 2000) showed that the fruit and vegetable diet reduced systolic blood pressure by 7.2 mm Hg and diastolic blood by 2.8 mm Hg (both $p<0.001$) compared to the control diet. A more detailed subgroup analysis of this study confirmed that the fruit and vegetable diet was more effective at lowering blood pressure among pre-hypertensive subjects than among those with normal blood pressure (Svetkey et al., 1999). A subsequent publication (Moore et al., 2001) reported that among DASH subjects with stage I isolated systolic hypertension (systolic blood pressure 140-159 mm Hg), the fruit and vegetable diet reduced systolic blood pressure to the normal range (i.e., <140 mm Hg) in 50% of the subjects (12 of 24). This reduction tended to be lower than that of the DASH diet (78%, 18 of 23), but was statistically similar ($p=0.07$). The control diet resulted in normal blood pressures in only 24% (6 of 25 subjects), which was less than the control group ($p<0.001$, χ^2). A separate publication (Obarzanek et al., 2001) reported that the fruit and vegetable diet lowered circulating T-C concentrations among DASH subjects by approximately 3 mg/dl versus the control diet, but the difference was not statistically significant (precise figures are not available because the data were presented graphically; however, the 95% CI appeared to be approximately -8 to 1.5 mg/dl). This diet resulted in a smaller reduction in LDL-C (~1.5 mg/dl) and no change in HDL-C concentrations. There was a borderline reduction in TG compared to the control diet (~9 mg/dL, $p = 0.055$). The last paper from the DASH trial that was identified (Chen et al., 2010) reported that although the fruit and vegetable diet significantly reduced systolic blood pressure compared to the control diet, and directionally improved diastolic blood pressure, it did not significantly lower T-C, LDL-C and TG concentrations. The estimated 10-year risk of CHD was reduced in all three groups compared to baseline, but the DASH diet was superior in this regard compared to both the fruit and vegetable diet ($p=0.012$) and the control diet ($p<0.001$). The fruit and vegetable diet decreased this parameter by 7% compared to the control group, but this result was not statistically significant. The intermediate response of the fruit and vegetable diet compared to the control and DASH diets for 10-year CHD risk reflected intermediate responses in blood pressure as well as serum lipid risk factors.

Smith-Warner et al. (2000) studied the effect of increasing fruit and vegetable intake for one year among 201 healthy subjects (30-74 years of age) who had been diagnosed with colorectal adenomatous polyps within the preceding five years. Baseline consumption among all participants was 4.0 servings of vegetables, 2.4 servings of fruit and 0.6 servings of juice. Total servings of fruits and vegetables increased by 4.7 servings per day in the experimental group and decreased by 0.5 servings per day in the control group ($p<0.001$). A wide range of fruits and vegetables was consumed by the participants in both groups, but there was higher ($p<0.001$) consumption in the experimental group of the following botanical subgroups: Compositae (e.g., lettuce), Cruciferae (e.g., broccoli), Leguminosae (e.g., beans), Liliaceae (e.g., onions), Rosacae (e.g., apples), Rutaceas (e.g., orange), Solanaceae (e.g, potatoes) and Umbelliferae (e.g., carrots). The only botanical subgroup that was not different between the two groups was Ericaceas (e.g., blueberries). Subjects in the fruit and vegetable group had lower serum T-C ($p<0.05$) and LDL-C

($p=0.02$) concentrations than those in the control group at the end of the one-year intervention. The experimental group also had higher serum concentrations of total carotenoids, α-carotene, ß-carotene, ß-crytoxanthin, lutein (all $p<0.001$) and lycopene ($p=0.014$) than the controls. There was no difference in blood pressure, which may have been due to the normotensive nature of the subjects (baseline blood pressures were approximately 127/76 mm Hg). There was also no difference in body weight or BMI between the two groups. This study provides additional evidence that increased consumption of fruits and vegetables, as a group, can beneficially affect CHD risk factors.

Broekmans et al. (2001) conducted a small ($n=48$) randomized, parallel study among apparently healthy subjects (40-60 years of age) living in the Netherlands. The control group consumed a diet low in fruits and vegetables (100 g/d) while the experimental group consumed 500 g fruits and vegetables and 200 ml fruit juice per day for four weeks. There were reductions ($p<0.05$) in both groups in serum lipid concentrations (T-C, LDL-C, HDL-C), but not in TG levels. Blood pressure, and a range of haemostatic variables (including fibrinogen), also decreased ($p<0.05$) in both groups. There were no overall treatment effects observed. This study does not provide evidence that fruits and vegetables, as a group, improve CHD risk factors, but the lack of statistical power and relative short intervention period may have contributed to this result. In addition, the applicability of the study to this proposed amendment would have been confounded by the provision of 200 ml fruit juice, which is not included in this proposed amendment.

John et al. (2002) studied the effect of an intervention designed to increase fruit and vegetable consumption for six months among healthy adults (25-64 years of age) living in the U.K. Subjects were randomly assigned to a fruit and vegetable group (n=344) or a control group (n=346) who were asked to maintain their habitual diet. The experimental group increased ($p<0.0001$) fruit and vegetable consumption by 1.4 servings per day at the end of the intervention compared to 0.1 serving per day among the controls. Plasma concentrations of α-carotene ($p=0.027$), ß-carotene ($p=0.005$), lutein ($p=0.032$), ß-cryptoxanthin ($p=0.0002$) and ascorbic acid ($p=0.023$) increased more in the experimental group than in the control group. There were no differences in such changes for lycopene, retinol, α-tocopherol and γ-tocohperol. There was also no difference in the change in serum T-C concentrations between the two treatments. However, systolic ($p<0.0001$) and diastolic ($p=0.02$) blood pressure were reduced more in the fruit and vegetable group than among control subjects. There were no significant changes in body weight. This study provides additional support for this proposed amendment because it showed that advice designed to increase fruits and vegetables, as a group, had a significant effect on a major CHD risk factor.

Dragsted et al. (2006) conducted a small (n=43) randomized, parallel design study to examine the effect of feeding 600 g/d fruits and vegetables, an equicaloric carbohydrate drink containing mixed sugars and citrate or a similar beverage supplemented with vitamins and minerals for 24 days. The subjects were free-living, healthy, normal weight adults (19-45 years of age) residing in Denmark. The exact composition of the fruits and vegetables provided was specified in a separate publication (Vogel et al., 2002) and included apple, pear, orange juice, carrot, broccoli, onion and tomato. The fruit and vegetable diet decreased plasma T-C and LDL-C concentrations (both $p<0.01$) with no change in HDL-C levels. There was also no change in body weight due to the interventions. This study provides additional evidence that fruits and vegetables, as a group, improve major CHD lipid risk factors.

Svendsen et al. (2007) conducted a randomized, parallel design intervention study among 35 women and 103 men (mean age = 48.2) with obesity (mean BMI = 36.7) for three months. All subjects were residents of Norway and had sleep-related breathing disorders. The subjects were randomly assigned to an intervention group and were instructed to increase fruit and vegetable intake by covering one half of their dinner plates with vegetables, one-quarter with potatoes, rice or pasta, and one quarter with meat, chicken, fish and/or legumes. Control subjects were given no dietary advice. Vegetable intake increased ($p<0.0001$) from 223 g/d to 457 g/d in the experimental group with no change in the control group. Fruit, juice and berry consumption also increased ($p<0.0001$) in the fruit and vegetable group from 242 to 486 g/d with no change among controls. Circulating concentrations of vitamin C ($p=0.0019$), ß-carotene ($p<0.0001$) and folate ($p<0.0001$) increased in the experimental group more than among control subjects. Systolic ($p=0.0022$) and diastolic ($p=0.012$) blood pressure was lower in the fruit and vegetable group than in the control group, despite being similar at baseline. Circulating TG concentrations decreased ($p=0.026$) more in the experimental group than the control group at the end of the intervention; however, there were no differences for T-C ($p=0.06$) or HDL-C ($p=0.14$). Interpretation of this study is complicated by the fact that subjects in the fruit and vegetable group lost 3.4 kg body weight ($p<0.0001$) during the intervention, while those in the control group did not ($p=0.14$). Nevertheless, the data show that increased intake of fruits and vegetables has a positive effect on CHD-related risk factors including obesity and blood pressure.

Hilpert et al. (2009) compared the effect of a diet rich in fruits and vegetables, a similar diet also rich in dairy products, and an average American diet on blood pressure and other parameters among 23 stage-I hypertensive (mean blood pressure = 140.5/91.1 mm Hg) adults (mean age = 45.3 years) using a randomized, cross-over design. The intervention periods were five weeks in duration separated by two-week wash-out intervals. All foods were provided and were adjusted in energy content to maintain constant body weight. The diets used menus similar to those employed in the DASH trials. The fruit and vegetable diet lowered systolic and diastolic blood pressure compared to the average American diet by 1.4 ($p<0.02$) and 1.8 mm Hg ($p<0.01$), respectively. Similar changes were observed for the fruit and vegetable diet with dairy foods. There were no significant differences in blood pressure response between these two fruit and vegetable containing diets.

McCall et al. (2009) studied the effect of diets containing graded amounts of fruits and vegetables (1, 3 and 6 portions/day) for eight weeks on endothelial function and other parameters among 117 hypertensive (mean blood pressure at baseline ~143/83 mm Hg) adults (mean age ~54 years) living in the U.K. A randomized cross-over design was used after a four-week run-in period during which the subjects consumed a diet that limited fruit and vegetable intake to one serving per day. The paper did not mention the use of wash-out periods. Data on composition of the diets (including the fruits and vegetables provided) were not given. Circulating concentrations of lutein (p=0.002) and ß-cryptoxanthin ((p<0.001) increased with increased vegetable consumption, but changes for vitamin C, zeaxanthin, α-carotene, ß-carotene and lycopene were not statistically significant. There were no significant treatment effects for systolic or diastolic blood pressure, circulating T-C:HDL-C ratio or TG concentrations. However, each portion of fruit and vegetable consumption resulted in a 6.2% improvement in forearm blood flow responses to intra-arterial administration of the endothelium-dependent vasodilator acetylcholine (p=0.03). The interpretation of this study is limited by the relatively low amounts of fruits and vegetables added to the diets. Six daily portions of these foods may not have been sufficient to elicit favorable changes in blood pressure or lipid risk factors. In addition, the sporadic increase in markers of fruit and vegetable intake (especially vitamin C and ß-carotene) suggest that lack of compliance and/or the low amount of fruits and vegetables provided may have reduced the likelihood of significant effects.

Berry et al. (2010) conducted a randomized cross-over study among 57 adult (mean age ~45 years) early hypertensive (mean blood pressure ~138/88 mm Hg) subjects living in the U.K. The study consisted of four, six-week treatment periods separated by five-week wash-out intervals. Subjects were randomly assigned to one of four groups: a control (habitual diet), 20 mmol potassium from fruits and vegetables, 40 mmol potassium from fruits and vegetables or a supplement of 40 mmol potassium. The fruits and vegetables were mainly provided from bananas, apples, citrus fruits, pears, plums, peaches, nectarines, dried fruit and berries (mainly strawberries), tomatoes, carrots, capsicum peppers, green vegetables (spinach, lettuce, cabbage and green beans) and mixed vegetables. Urinary potassium was higher ($p=0.0001$) and the ratio of urinary sodium to potassium was lower ($p=0.008$) after the three experimental diets versus the control diet, but there were no significant differences in plasma α- or ß-carotene, vitamin C or serum folate after the fruit/vegetable-containing and non fruit/vegetable-containing treatments. The paper stated that the lack of an effect for vitamin C was not surprising because the subjects were non-smokers and habitual consumption of this nutrient is high in the U.K. Likewise, the authors stated the lack of an effect for folate was expected because the fruits and vegetables used in the study were not high in this vitamin. Nevertheless, the data do not convincingly confirm adherence to the diets with respect to fruit and vegetable intake. No treatment effects were observed in the study. The null findings included the primary endpoint of blood pressure. Secondary outcome measures for which there was no response included serum T-C, LDL-C, HDL-C, TG, intracellular adhesion molecule-1, as well as plasma insulin, glucose, homocysteine, C-reactive protein and 8-isoprostane $F_{2\alpha}$. This study appeared to be well designed; however, specifics of composition of the diet, including the quantity of fruits and vegetables consumed, were not provided. In addition, as noted above, there was some suggestion of poor compliance.

3. Intervention studies on CHD biomarkers for individual fruits and vegetables affected by the proposed amendment

Separate literature searches were conducted to identify human studies that examined the cardioprotective properties of the fruits and vegetables that would become eligible for the dietary saturated fat and cholesterol and risk of CHD health claim under the proposed amendment to the governing regulation. No attempt was made to identify such studies for fruits and vegetables that already qualify for this claim.

The purpose of this analysis was to determine if exclusion of such fruits and vegetables is justified by scientific evidence that suggests they would compromise the cardioprotective effects of a diet low in saturated fat and cholesterol. Such data, if observed consistently, would provide credence for the exclusion of fruits and vegetables that do not satisfy "low-fat" and/or 10% DV minimum nutrient content requirements. No evidence of such an effect was identified, as discussed in the following section.

a) Avocado studies

By far the greatest number of studies found among the fruits and vegetables considered in this section were conducted with avocados. These studies are discussed below in chronological order by year of publication.

Grant (1960) examined 16 male subjects (age range = 27-72 years) living in a veterans hospital in Florida. Three of the subjects had diabetes, five were consuming a "salt-restricted" diet (5 to 10 g/d), and the remainder were eating a standard hospital diet. All subjects consumed their habitual diet without avocados during the control phase of the study, which lasted until "reasonably constant fasting blood levels" were obtained (8 to 56 days). Avocados (0.5 to 1.5 per day) were then added to the diet. Animal fat equivalent to half or more of the avocado lipid was removed from the basal diet of all but one subject (i.e., avocado replaced part of the saturated fat in the diets of these subjects). No such adjustment was made for the remaining subject. The intervention period was not specified numerically, but it appeared to be about 25 days based on a graphic representation of the study design. Fasting lipids were taken at the end of the control and avocado periods. T-C concentrations decreased significantly in eight of the 16 subjects ($p= <0.01$ to <0.02), but there were no significant changes in the remaining subjects. None of the subjects experienced a significant increase in circulating T-C levels. Summary statistics (i.e., mean, standard deviation, p-value) were not provided. Means calculated from the individual results provided for the control and avocado periods were 297 and 225 mg/dl, respectively (p-value calculated from the individual data using 2-tailed t-test = 0.17). Two subjects were continued for an additional cycle of habitual and avocado-containing diets, but data on lipids and other parameters were not provided. The paper reported that average body weight did not change significantly, but no summary data or statistics were provided. The results of this uncontrolled, open-label study are difficult to interpret due to design limitations and lack of dietary and other data; nevertheless, it provides no evidence to suggest that avocados should be excluded from the dietary saturated fat and cholesterol and risk of CHD health claim.

Alvizouri-Munoz et al. (1992) studied the effect of two-week supplementation with avocado on plasma lipids among 16 healthy (mean BMI = 22.9), normolipemic (baseline T-C = 114 mg/dL) Mexican women (n=7) and men 18-37 years of age. A randomized, cross-over design was used and subjects consumed their habitual diet at the beginning of the study. It appears that a five-day run-in period using this diet was employed as the control treatment, but the paper was not clear on this point. Subjects were randomized to one of three diets: A MUFA-enriched, controlled diet (all foods provided and consumed under supervision) (RMF) with 30% en fat (22.5% en as avocado lipid), 50% en carbohydrate and 20% en protein; a low-saturated fat controlled diet (LSF) with 20% en fat (from meat and safflower oil), 60% en carbohydrate and 20% en protein with no avocado; or a free MUFA-enriched diet (FME) in which the same amount of avocado as the RMF diet was provided, but all foods except the avocado were eaten under free-living *ad libitum* conditions. The RMF and LSF diets contained less than 300 mg cholesterol. Fasting blood samples were obtained at the beginning and end of each two-week treatment period. The saturated fat content and other diet composition data were not provided. Body weight was 1.6 and 0.8 kg lower after the RMF and LSF diets versus the control (baseline) diet (both $p<0.01$). Compared to the control, the RMF diet resulted in lower ($p<0.05$) plasma LDL-C, but there were no differences in T-C, HDL-C, or TG concentrations. There were no differences between the RMF and FME diets in these parameters; however, the LSF diet resulted in lower T-C, LDL-C, and HDL-C than the control diet. The FME diet also lowered HDL-C concentrations compared to the control treatment. Comparative statistics were not provided between the LSF and RMF diets (the two treatments where all foods were provided); however, the authors observed, "Effects of the lipid profile appeared to be better with a low-saturated fat diet enriched with avocado than those obtained with a low-saturated fat diet alone. This latter diet showed two important disadvantages: increase in triacylglycerol and decrease in HDL cholesterol levels, which may counteract the beneficial actions on total and LDL cholesterol." The interpretation of this study is limited by the short intervention periods, lack of dietary information on concentration of saturated fat and other nutrients, and weight loss that occurred in two of the treatments. Nevertheless, this study provides suggestive evidence that avocados are beneficial as part of a diet low in saturated fat and cholesterol. The results are also impressive because the subjects were normocholesterolemic at baseline.

Colquhoun et al. (1992) studied the effect of avocado consumption as part of a moderate-fat (36.8% en) diet relatively low in saturated fat (10.75% en) compared to a low-fat (20.8% en), low saturated fat (7.19% en) diet for three weeks among 15 Australian women (37-58 years of age). A randomized, cross-over design with a three-week run-in period (during which a habitual diet was consumed) was used. The paper did not mention the use of a wash-out period between treatments. The avocado diet lowered circulating T-C ($p<0.05$) and LDL-C ($p<0.01$) concentrations compared to baseline with no change in HDL-C. These parameters did not change from baseline for the low-fat diet, but there was a decrease ($p<0.01$) in HDL-C levels. Neither diet resulted in a change in TG concentrations. Statistics that compared lipid values at the end of both treatments were not provided. The authors noted, "This study provides further evidence that foods rich in monounsaturated fatty acids are suitable as a substitute for dietary saturated fatty acids in cholesterol-reducing diets. At the same time, such a diet does not lower the HDL-lipoprotein or apolipoprotein A-I."

Lerman-Garber et al. (1994) studied 12 overweight (mean BMI = 28) women (mean age = 56 years) with well-controlled, non insulin-dependent type-2 diabetes, who consumed a high MUFA diet (40% en total fat, 24% en MUFA, 11% en saturated fat) with one avocado and four teaspoons of olive oil per day, or a low-fat (30% en, 6.6% en MUFA, 6.6% en saturated fat) high-carbohydrate diet for four weeks. A randomized, cross-over design with four-week run-in, intervention and wash-out periods was employed. T-C concentrations decreased ($p<0.05$) compared to baseline for both treatments with no difference between diets. No changes from baseline were observed for circulating LDL-C or HDH-C; however, TG levels decreased ($p<0.05$) after the avocado-containing diet, but not after the high-carbohydrate regimen. There was also a significant treatment effect between the two diets for this parameter ($p<0.05$).

Lopez Ledesma et al. (1996) conducted a seven-day, controlled-feeding study (hospitalized patients with all food provided) among 30 young (mean age = 22 years) normocholesterolemic (mean serum T-C < 200 mg/dL) Mexicans and 37 volunteers (35-65 years of age) with "moderate" hypercholesterolemia (mean serum T-C = 210-358 mg/dL). Fifteen of the hypercholesterolemic subjects had type-2 diabetes. The normocholesterolemic subjects were randomly assigned to a high-MUFA (22% en), high-fat (53% en), high saturated fat (18.4% en) diet that contained 300 g of avocado per day. The avocado was added to the diet as a substitute for other lipid sources. A control diet that was also high in total fat (52% en) and saturated fat (20.0% en) with somewhat lower MUFA content (14.5% en) was also provided. Fifteen hypercholesterolemic subjects were assigned to the avocado-rich diet and seven were assigned to the control diet. The remaining 15 subjects with diabetes were assigned to the avocado-rich diet. Among the normocholesterolemic subjects, serum T-C decreased compared to baseline in both groups ($p<0.01$), while serum LDL-C decreased only during the avocado-rich diet ($p<0.01$). Both T-C and LDL-C were lower ($p<0.01$) after the avocado-rich diet than after the control diet. Serum TG concentrations also decreased during the avocado-rich diet ($p<0.01$), but not after the control diet. There was no treatment effect between the two diets in this parameter. Among the hypercholesterolemic subjects, serum T-C, LDL-C and TG levels decreased ($p<0.01$) versus baseline on the avocado-rich diet among both subjects with and without diabetes. In addition, all three of these parameters were lower at the end of the intervention in the avocado-rich diet than they were after the control diet ($p<0.01$). The authors concluded, "High lipid, high MUFA-avocado enriched diet can improve lipid profile in healthy and especially in mild hypercholesterolemic patients, even if hypertriglyceridemia (combined with hyperlipidemia) is present." This paper is limited by the short intervention period and lack of assignment of subjects with diabetes to the control diet. Nevertheless, it provides suggestive evidence that avocados are hypocholesterolemic when substituted for other sources of dietary fat.

Carranza-Madrigal et al. (1997) studied 13 Mexican females (n=11) and males (mean age = 55.8 years) with moderate hypercholesterolemia (mean circulating T-C = 267, LDL-C = 176, TG = 184 mg/d) and moderate overweight (mean BMI = 28.7). The subjects discontinued lipid-lowering drugs four weeks prior to being randomized to one of three diets for four weeks each: An avocado-free vegetarian diet (ALVD) (70% en carbohydrate, 10% en protein, 20% en fat), an avocado-containing vegetarian diet (AVD) (60% en carbohydrate, 10% en protein and 30% en fat [including 22.5% en from avocado lipid]) or a "free" diet with avocado (FDWA), which provided the same amount of avocado as the AVD, but the subjects were free to choose all other foods. No information on the nutritional composition of the control (baseline) or free-living diets were provided. All foods were furnished and consumed under supervision for the ALVD and AVD. Body weight and BMI decreased by 0.72 kg and 0.3 kg/m^2, respectively (both $p<0.05$), after the avocado-free diet (ALVD) compared to the control diet. Body weight was also 0.2 kg ($p<0.05$) higher after the free-living avocado diet (FDWA) than after the ALVD); however, there were no differences in BMI between these two treatments. The physiological relevance of these small statistically significant changes is unclear. The avocado-containing controlled vegetarian diet (AVD) was the only treatment that lowered serum LDL-C concentrations versus the control ($p<0.05$). All three diets lowered HDL-C compared to baseline ($p<0.05$); however, this parameter was higher after both avocado-containing diets than after the avocado-free diet ($p<0.05$). The free-living, avocado-containing diet (FDWA) resulted in higher ($p<0.05$) T-C and LDL-C concentrations than the controlled avocado-containing diet (AVD); however, the cause of this difference is difficult to assess because the saturated fat and other composition data of the free-living diet were not provided. The results of this study are difficult to interpret due to lack of information about the composition of the control and free-living diets. Nevertheless, the findings suggest that a vegetarian, avocado-containing diet may result in lower serum

LDL-C and higher HDL-C concentrations than a similar diet without avocados, and provide no basis to exclude avocados from the dietary saturated fat and cholesterol and risk of CHD health claim.

The most recent study identified that examined the effect of avocados on CHD-related risk factors was a six-week, randomized, controlled parallel study among 61 overweight (mean BMI = 31.9) free-living women (n=48) and men (mean age = 40.8 years) residing in South Africa (Pieterse et al., 2005). Baseline values for serum T-C, LDL-C and TG were 201, 134, and 179 mg/dL, respectively). The subjects were randomly assigned to one of two isocaloric, energy-restricted diets that provided 55% en carbohydrate, 30% en fat and 15% en protein (no data were provided on actual energy intake or the level of energy restriction of these diets). The experimental diet provided 200 g avocado (containing 30.6 g fat) per day, which was substituted for 30 g of fats from mixed sources including margarine and oil. The control diet did not contain avocados. Four participants in the avocado group and two in the control group were taking cholesterol-lowering drugs during the study. Both groups lost weight ($p<0.001$) with no difference between groups. T-C, LDL-C, HDL-C and TG did not change during the intervention period in either group, and there were no treatment effects between groups. The authors concluded that the consumption of 200 g/d of avocado within an energy-restricted diet does not compromise weight loss when substituted for 30 g of mixed dietary fat. This study is difficult to interpret because it was conducted under weight-loss conditions that may have obscured any effect of avocados on blood lipids, and some of the subjects were taking lipid-lowering drugs.

b) Studies with other fruits or vegetables

Only three studies in healthy humans were identified that were conducted on fruits and vegetables other than avocados that would be affected by the proposed amendment. Karlander et al. (1991) studied the effect of supplementing the diet of 13 non-insulin dependent diabetic subjects (mean age ~58 years, mean BMI ~30) with 16 g/d beet fiber for six weeks using a randomized, cross-over design. The subjects were assigned to a diet recommended for control of diabetes that contained beet fiber or a similar diet without beet fiber. The control diet was consumed by both groups during a six-week run-in period. Serum T-C was lower ($p<0.001$) after the beet fiber-containing diet among eight subjects who were taking sulfonylurea to manage their diabetes, but not among five patients who were controlling this condition with diet alone. There were no diet-related differences in serum TG concentrations. No data for other blood lipids were reported. The conclusions that can be drawn from this small study are limited because it examined beet fiber rather than raw beets. Nevertheless, this study provides indirect evidence that beets may be hypocholesterolemic among certain patients with diabetes.

Larmo et al. (2009) studied the effect of sea buckthorn berries on blood lipids among 229 healthy subjects 19-50 years of age. The participants were randomly assigned to consume 28 g/d of sea buckthorn berries or a placebo for three months. The experimental group had increased concentrations of quercetin ($p=0.03$), kaempferol ($p=0.08$) and isorhamnetin ($p<0.01$) compared to the control group, but there were no differences in serum T-C, LDL-C, HDL-C or TG between the two groups. This study shows that sea buckthorn berries do not improve serum lipids when added to a habitual diet, but provides no evidence to suggest that this fruit would compromise the ability of a diet low in saturated fat and cholesterol to do so.

Park and Jhon (2009) studied the effect of bamboo shoot consumption among eight healthy (mean BMI = 20.2) Korean women 21-23 years of age. The study used a sequential design that provided a diet containing 28 g cellulose for six days, followed by a low-fiber (6 g/d) control diet for six days and finally a diet that contained 360 g boiled bamboo shoots (28 g fiber) for an equal duration. The three diets were similar in energy, protein, fat and carbohydrate content. The bamboo shoot diet resulted in lower serum T-C ($p<0.05$) than the other two treatments. Serum LDL-C was lower ($p<0.05$) after the bamboo shoot treatment than after the control diet, but was no different from the high-cellulose regimen. Serum HDL-C concentrations were lower ($p<0.05$) after the control and bamboo shoot treatments than after the cellulose diet. The authors concluded that bamboo shoots have beneficial effects on serum lipids. This study is difficult to interpret because the six-day intervention period is insufficient to stabilize blood lipid concentrations. Nevertheless, this study provides no evidence to suggest that bamboo shoots should be excluded from the dietary saturated fat and cholesterol and risk of CHD health claim.

A study designed to examine the effect of oyster mushroom consumption on CHD-related risk factors and other biological markers in hyperlipidemic subjects with diabetes was also identified (Khatun et al., 2007). This study is not directly applicable to the proposed amendment because it was conducted in unhealthy individuals; however, it is noted here in an effort to provide FDA with the totality of scientific evidence. The study employed 89 subjects with diabetes (fasting plasma glucose >144 mg/dL) (mean age = 46.3 years) who participated in three sequential seven-day treatments. The first treatment provided 50 g cooked oyster mushrooms (*Pleurotus ostreatus*) three times per day added "as part of vegetable" followed by a wash-out period without mushrooms. A third mushroom treatment, identical to the first, was then provided. Measurements were taken at baseline and at the beginning and end of the three intervention periods. Comparisons were provided between mushrooms and no-mushroom treatments. There were significant decreases after the first mushroom intervention in plasma T-C ($p=0.002$) and TG ($p<0.001$) concentrations with no change in HDL-C. Systolic and diastolic blood pressures were also reduced ($p=0.003$ and $p=0.01$, respectively). Removal of mushrooms resulted in a reversal of these results, and re-introduction of mushrooms once again resulted in significant decreases in plasma T-C ($p<0.001$) and TG ($p=0.05$) concentrations as well as a reduction in diastolic blood pressure ($p=0.017$). There were no changes in body weight throughout the experiment. This study is limited by the non-randomized nature of the design, lack of dietary information, the large dose of mushrooms employed, and the fact that only 30 of 89 subjects completed the trial (34%). Nevertheless, it provides no scientific evidence for the exclusion of mushrooms from the dietary saturated fat and cholesterol and reduced risk of CHD health claim due to failure to meet the 10% DV minimum nutrient content requirement.

E. Dietary fat and risk of CHD

It is now well accepted that total dietary fat is not associated with, or causally related to, CHD. Numerous governmental and non-governmental dietary recommendations acknowledge this fact, including the *DGA* (U.S. Department of Agriculture and U.S. Department of Health and Human Services) and the Food and Agriculture Organization/World Health Organization (FAO/WHO) (2011). A more thorough discussion of these recommendations is presented Section IV below. In addition, FDA has established a strong precedent that total dietary fat within the recommended range is not related to CHD by granting exemptions to the low-fat and/or total fat disqualifier levels for multiple health claims, as discussed in Section V. Therefore, no attempt was made to provide a comprehensive summary of the scientific evidence that led to these positions. Nevertheless, the most recent systematic reviews/meta-analyses of prospective cohort studies (Skeaff and Miller, 2009) and dietary intervention studies (Hooper et al., 2011) that examined the relationship between total fat and CHD are presented below as an indication of the consistency of the available scientific evidence.

Skeaff and Miller (2009) pooled data from 28 individual cohort studies that examined 280,000 subjects during approximately 3.7 million person-years of follow-up. There were approximately 6,600 CHD deaths during this period, which ranged from four to 25 years among the studies. Total fat was not associated with CHD mortality (RR=0.94; 95% CI, 0.74-1.18) or CHD-related events (RR=0.93; 95% CI, 0.84-1.03). An increment of 5% en from total fat was also not associated with increased CHD deaths (RR=1.06; 95% CI, 0.88-1.28) or events (RR=1.02; 95% CI, 0.98-1.05). These data clearly demonstrate that the available prospective cohort data show that dietary fat is not associated with the risk of CHD.

Similar results were reported in a recent Cochrane review entitled, "Reduced or modified dietary fat for preventing cardiovascular disease" (Hooper et al., 2011). This review included 48 randomized, controlled human intervention trials that reported CHD incidence and mortality. There was no effect of any dietary fat intervention compared to habitual or control diets (RR=0.98; 95% CI, 0.93-1.04) on CHD mortality based on data from 71,790 participants and 4,292 deaths. Furthermore, there was no such effect on incidence of MI (RR=0.93; 95% CI, 0.84-1.02) based on 64,891 subjects and 2,068 events. The authors concluded, "The findings are suggestive of a small but potentially important reduction in cardiovascular risk on modification of dietary fat [e.g., saturated fat], but not reduction of total fat, in longer trials. Lifestyle advice to all those at risk of cardiovascular disease and to lower risk population groups, should continue to include permanent reduction of dietary saturated fat and partial replacement by unsaturates. The ideal type of unsaturated fat is unclear."

F. Discussion and conclusions

AHA strongly believes the scientific evidence presented above supports the proposed amendment. This evidence clearly shows that fruits and vegetables, as a group, have many nutritional benefits and are associated with reduced risk of CHD (and more broadly with CVD). In addition, controlled feeding studies confirm that increased intake of fruits and vegetables, as a group, favorably affects FDA-accepted CHD-related biomarkers.

Data pertaining to the fruits and vegetables that are directly affected by this proposed amendment reveal no evidence to suggest interference with the hypocholesterolemic effect of diets low in saturated fat and cholesterol, and suggestive evidence that they may be cardioprotective in their own right (especially avocados). In conclusion, no evidence was found from the scientific literature that fruits and vegetables that do not meet the low fat definition or those that fail to meet the 10% DV minimum nutrient content requirement for health claims should be excluded from the dietary saturated fat and cholesterol and risk of CHD health claim. This conclusion is based on the following observations.

Scientific evidence supports recommendations from the *DGA* (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2010) and other governmental and professional organizations for increased consumption of fruits and vegetables, as a group, based on their beneficial associations/effects related to obesity, diabetes, metabolic syndrome and numerous cancer sites as well as CHD/CVD.

Observational data provide strong support for the proposed amendment. These data are exceptionally consistent for the association between fruits and vegetables, as a group, and stroke. Six prospective cohort studies (Bazzano et al., 2002, Gillman et al., 1995, Hirvonen et al., 2000, Johnsen et al., 2003, Joshipura et al., 1999, Sauvaget et al., 2003) and one case-control study (Mahe et al., 2010) reported significant protective associations for fruits and/or vegetables, as a group, and stroke. Only two small prospective studies failed to report such an association (Keli et al., 1996, Steffen et al., 2003). The consistency of these findings was confirmed by two meta-analyses (Dauchet et al., 2005, He et al., 2006). Stroke is not a condition reflected in the dietary saturated fat and cholesterol and risk of CHD health claim, but it is closely related to this claim because both CHD and stroke are important components of CVD.

The observational data for CHD *per se* also provide consistent support for the proposed amendment. Fifteen studies (13 prospective cohort and two case-control) that examined 681,346 subjects with a mean follow-up period of 13.0 years (range = 5.0 to 37 years) were identified. Six prospective cohort studies among 475,131 subjects with an average follow-up period of 12.0 years (range = 5.4 to 20 years) (Crowe et al., 2011, Dauchet et al., 2007, Hirvonen et al., 2001, Joshipura et al., 2001, Knekt et al., 1996, Tucker et al., 2005) and two case-control studies (Yusuf et al., 2004, Lanas et al., 2007) reported fully adjusted significant inverse associations between fruit and/or vegetable consumption, as a group, and risk of CHD. Three additional prospective studies reported similar associations for age and gender-adjusted associations, but not for more fully corrected associations (Liu et al., 2000, Steffen et al., 2003, Takachi et al., 2008). Only four prospective studies failed to report significantly protective associations. Furthermore, none of these studies reported associations in the positive direction (Bazzano et al., 2002, Liu et al., 2000, Mann et al., 1997, Ness et al., 2005). The consistency of inverse associations between fruit and/or vegetable consumption and CHD reported by the observational data are reflected in two recent meta-analyses (Dauchet et al., 2006, He et al., 2007). Both of these publications showed that pooled data from the prospective cohort studies found significant protective associations for fruits and vegetables as a single group, as well as for each group considered individually. The interpretation of observational studies is limited by the potential for both under- and over-adjustment and the possibility of unknown confounding variables. Nevertheless, the studies identified in this section provide strong, consistent support for the proposed amendment and no evidence of unfavorable associations with increased fruit or vegetable consumption. Five observational studies that were not previously discussed were identified that examined the possible association between fruit and/or vegetable fiber and CHD (Fehily et al., 1993, Liu et al., 2002, Mozaffarian et al., 2003, Pietinen et al., 1996, Rimm et al., 1996). These studies showed that fruit and vegetable fiber consumption was not consistently associated with multivariate-adjusted CHD risk. A meta-analysis of prospective cohort studies published in 2004 (Pereira et al.) observed that pooled data for 10 g increments of fiber from fruit was inversely associated with all coronary events (RR=0.70; 95% CI, 0.55-0.89), but vegetable fiber was not (RR=1.00; 95% CI, 0.82-1.23). Similar associations were observed for CHD deaths. These data suggest that the protective properties of fruits and vegetables (especially vegetables) involve constituents other than dietary fiber. Therefore, in the case of the dietary saturated fat and cholesterol and risk of CHD health claim, the fiber component of the 10% DV minimum nutrient content requirement does not appear to be predictive.

Occasional instances where vegetables that do meet the 10% DV minimum nutrient content and/or low-fat requirements were not associated with reduced risk of CHD. Specifically, Mann et al. (1997) reported that consumption of carrots was not associated with IHD mortality among 10,802 subjects followed for an average of 13.3 years

(RR=0.76; 95% CI, 0.37-1.75; p for trend NS). Furthermore, Joshipura et al. (2001) observed a similar result for potato consumption among 84,251 women from the Nurses' Health Study followed for 14 years and 42,148 men from the Health Professionals' Follow-Up Study followed for eight years (RR=1.06; 95% CI, 0.78-1.70). These isolated findings do not prove that carrots and/or potatoes are not cardioprotective in the context of a diet low in saturated fat and cholesterol, but they do show that compliance with the 10% DV minimum nutrient content requirement does not ensure such a finding.

Twelve controlled-feeding studies that examined fruits and/or vegetables as a group were identified. These studies examined a total of 1,902 subjects with an average intervention period of 11.5 weeks (range = two to 52 weeks). Eight of these studies (Appel et al., 1997, Broekmans et al., 2001, Dragsted et al., 2006, Grande et al., 1974, Hilpert et al., 2009, John et al., 2002, Smith-Warner et al., 2000, Svendsen et al., 2007) reported that fruits and vegetables significantly lowered blood pressure or had beneficial effects on lipid risk factors for CHD. The studies that failed to report such findings tended to lack statistical power or were difficult to interpret due to possible poor compliance or failure to provide enough fruits and vegetables to elicit an effect. Many of the fruits and vegetables that would be affected by the proposed amendment were likely included in these studies as part of the overall fruit and vegetable interventions. For example, cucumbers were included in the DASH diet[4] and three of the studies cited above (Fraser et al., 1981, Grande et al., 1974, Smith-Warner et al., 2000) specifically noted providing beets, celery, grapes or lettuce.

[4] Personal communication from Dr. Lawrence Appel, July 12, 2012

Seven dietary intervention studies among 200 subjects with an average intervention period of 3.4 weeks (range = one to six weeks) were identified that examined the effect of avocado-containing diets on lipid-based risk factors for CHD. Five of these studies (Alvizouri-Munoz et al., 1992, Carranza-Madrigal et al., 1997, Colquhoun et al., 1992, Lerman-Garber et al., 1994, Lopez Ledesma et al., 1996) reported that avocado consumption had beneficial effects on such risk factors either compared to baseline or to a non-avocado containing diet. Nevertheless, conclusions that can be drawn from these studies are limited by a variety of quality and methodological issues including intervention times of less than three weeks, use of lipid-lowering drugs, small sample size, subjects with extreme hypercholesterolemia or other health-related conditions, and lack of information on the composition of the diets provided. Only two intervention studies that fed avocados reported no significant changes in blood lipids. Grant (1960) reported no overall treatment effect among 16 veterans hospital residents, but the study did not include a control diet, and Pieterse et al. (2005) found no effect on serum lipid concentrations among 61 overweight subjects, but weight loss prompted by energy restriction may have confounded the results. Collectively, these studies provide no scientific evidence for the exclusion of avocados from the dietary saturated fat and cholesterol and risk of CHD health claim. In fact, such studies suggest that avocados, in their own right, may be hypocholesterolemic.

Studies that examined the effect of beet fiber (Karlander et al., 1991), sea buckthorn berries (Larmo et al., 2009) and bamboo shoots (Park and Jhon, 2009) also provided no evidence that these foods should be excluded from the dietary saturated fat and cholesterol and risk of CHD health claim.

No studies were identified that examined the effect of cucumbers, grapes, iceberg lettuce, mushrooms, plumbs, scallions or sweet corn on blood lipids in healthy humans. Nevertheless, one study with oyster mushrooms (Khatun et al., 2007) as well as review papers that summarized considerable information on the cardioprotective properties of mushrooms (Guillamon et al., 2010) and grapes (albeit mostly from studies on juice, wine or seeds) (Bertelli and Das, 2009, Perez-Jimenez and Saura-Calixto, 2008, Vislocky and Fernandez, 2010) have been published. The absence of studies on these fruits and vegetables confirms that there is no scientific evidence to support their exclusion from the dietary saturated fat and cholesterol and risk of CHD health claim. AHA strongly contends that in the absence of such evidence, there is no credible reason to believe that such fruits and vegetables would compromise the ability of a low-saturated fat diet to have a favorable effect on risk of CHD.

Finally, there is a clear consensus that total fat intake is not associated with CHD incidence based on the available prospective cohort studies (Skeaff and Miller, 2009). In addition, a very recent systematic review of the available controlled intervention studies (Hooper et al., 2011) concluded that there is no causal effect of dietary fat on CHD incidence or mortality. A very recent review paper by Willett (2012) also emphasizes this point. The AHA strongly believes that this evidence shows that fruits and vegetables that do not meet the "low-fat" definition should not be excluded from the dietary saturated fat and cholesterol and risk of CHD health claim.

IV. PUBLIC HEALTH RECOMMENDATIONS

A. Introduction

Numerous governmental, professional and public health organizations have issued specific guidelines and recommendations regarding fruit and vegetable consumption and total fat content of the diet. These recommendations overwhelmingly encourage increased consumption of fruits and vegetables without regard to their total fat or micronutrient content. In addition, these organizations have concluded that moderate fat, rather than low-fat, intakes are beneficial as part of a diet designed to manage the risk of CHD and other chronic health conditions. These recommendations are summarized in the following section.

B. Governmental organizations

Recommendations from federal agencies of the U.S. government (especially the 2010 *DGA*) are particularly germane to the proposed amendment because they represent official nutrition policy. Title 7 of the U.S. Code § 5341(a)(1) requires that any dietary guidance for the general population or identified population subgroups shall be reviewed by the secretaries of Health and Human Services and the U.S. Department of Agriculture to ensure consistency with the *DGA*.

1. *Dietary Guidelines for Americans*

Fruits and vegetables are among the most highly recommended foods in the 2010 *DGA*. Fruits are mentioned 69 times and vegetables 113 times. These foods, as a group, are recommended for their micronutrient content, their potential to reduce the risk of CVD and some cancers, as well as for their relatively low energy content. The specific language states,

> "Three reasons support the recommendation for Americans to eat more vegetables and fruits. First, most vegetables and fruits are major contributors of a number of nutrients that are underconsumed in the United States, including folate, magnesium, potassium, dietary fiber, and vitamins A, C, and K. Several of these are of public health concern for the general public (e.g., dietary fiber and potassium) or for a specific group (e.g., folic acid for women who are capable of becoming pregnant).
>
> Second, consumption of vegetables and fruits is associated with reduced risk of many chronic diseases. Specifically, moderate evidence indicates that intake of at least 2 ½ cups of vegetables and fruits per day is associated with a reduced risk of cardiovascular disease, including heart attack and stroke. Some vegetables and fruits may be protective against certain types of cancer.
>
> Third, most vegetables and fruits, when prepared without added fats or sugars, are relatively low in calories. Eating them instead of higher calorie foods can help adults and children achieve and maintain a healthy weight."

These recommendations echo the principle behind the proposed amendment because several of the nutrients for which fruits and vegetables are noted as sources are not those included in the 10% DV minimum nutrient content requirement (i.e., magnesium, potassium, vitamin D and folic acid). These guidelines also specifically mention the cardioprotective properties of fruits and vegetables as a group.

The 2010 *DGA* also specifically conclude that *all* fruits and vegetables are nutrient dense foods when prepared without added solid fats or sugars. This statement applies to fruits and vegetables, as a group, without regard to the 10% DV minimum nutrient content requirement,

> "Nutrient-dense foods and beverages provide vitamins, minerals, and other substances that may have positive health effects with relatively few calories. The term "nutrient dense" indicates that the nutrients and other beneficial substances in a food have not been "diluted" by the addition of calories from added solid fats, added sugars, or added refined starches, or by the solid fats naturally present in the food. Nutrient-dense foods and beverages are lean or low in solid fats, and minimize or exclude added solid fats, sugars, starches, and sodium. Ideally, they also are in forms that retain naturally occurring components, such as dietary fiber. **All vegetables, fruits, whole grains, seafood, eggs, beans and peas, unsalted nuts and seeds, fat-free and low-fat milk and milk products, and lean meats and poultry—when prepared without adding solid fats or sugars—are nutrient-dense foods."** (emphasis provided)

The 2010 *DGA* also recommend moderate fat (rather than low fat) consumption according to the Acceptable Macronutrient Distribution Range (AMDR) of 20-35% of energy established by the IOM (2002).

> "Dietary fats are found in both plant and animal foods. Fats supply calories and essential fatty acids, and help in the absorption of the fat-soluble vitamins A, D, E, and K. The IOM established acceptable ranges for total fat intake for children and adults (children ages 1 to 3 years: 30–40% of calories; children and adolescents ages 4 to 18 years: 25–35%; adults ages 19 years and older: 20–35%) ...These ranges are associated with reduced risk of chronic diseases, such as cardiovascular disease, while providing for adequate intake of essential nutrients. Total fat intake should fall within these ranges."

Furthermore, the *DGA* specify that unsaturated fats (including MUFA, which are the predominant fatty acid class in avocados), should replace solid fats in the diet.

Specifically, the guidelines recommend, "Consume less than 10 percent of calories from saturated fatty acids by replacing them with monounsaturated and polyunsaturated fatty acids." The guidelines also state,

> "Fats with a high percentage of monounsaturated and polyunsaturated fatty acids are usually liquid at room temperature and are referred to as 'oils'… Oils are not a food group, but are emphasized because they contribute essential fatty acids and vitamin E to the diet. Replacing some saturated fatty acids with unsaturated fatty acids lowers both total and low-density lipoprotein (LDL) blood cholesterol levels….Oils are naturally present in foods such as olives, nuts, avocados, and seafood."

In summary, the *DGA* provide no rationale for the exclusion of fruits and vegetables that fail to meet the 10% DV minimum nutrient content or "low-fat" criteria currently required under 21 C.F.R. § 101.75, and considerable information that all such foods be included. Specifically, these guidelines indicate that consumption of all fruits and vegetables should be increased and that all such foods are nutrient dense when prepared without added solid fats or sugars, as would be the case under the proposed amendment. In addition, the *DGA* indicate that moderate fat diets in which oils rich in MUFA and PUFA (from sources such as avocados) replace saturated and *trans* fatty acids are recommended for their cardioprotective properties.

2. MyPlate

MyPlate is based on the *DGA* and is intended to translate these guidelines to consumers in the form of an understandable, personalized eating plan. Accordingly, MyPlate encourages consumers to cover half of their plate with fruits and vegetables as a group.

The raw fruits and vegetables that would become eligible for the dietary saturated fat and cholesterol and risk of CHD health claim under the proposed amendment that are specifically listed by MyPlate are avocados, beets, cucumbers, grapes, iceberg lettuce, mushrooms, plums and sweet corn.[5]

The specific health benefits of consuming the amount of fruits and vegetables recommended by MyPlate are listed below.[6]

- Eating a diet rich in vegetables and fruits as part of an overall healthy diet may reduce risk for heart disease, including heart attack and stroke.
- Eating a diet rich in some vegetables and fruits as part of an overall healthy diet may protect against certain types of cancers.
- Diets rich in foods containing fiber, such as some vegetables and fruits, may reduce the risk of heart disease, obesity, and type 2 diabetes.
- Eating vegetables and fruits rich in potassium as part of an overall healthy diet may lower blood pressure, and may also reduce the risk of developing kidney stones and help to decrease bone loss.
- Eating foods such as vegetables that are lower in calories per cup instead of some other higher-calorie food may be useful in helping to lower calorie intake.

MyPlate also informs consumers that fruits and vegetables are important sources of nutrients often consumed in insufficient amounts such as dietary fiber, calcium, folic acid, potassium, vitamin A and vitamin C. Similar to the *DGA*, these nutrients are not restricted to those included in the 10% DV minimum nutrient content requirement.

Also similar to the DGA, MyPlate does not recommend restriction of total fat; but advises consumers to limit consumption of solid fats and *trans* fats. Oils are defined as,

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[5] http://www.choosemyplate.gov/food-groups/fruits.html
http://www.choosemyplate.gov/food-groups/vegetables.html
[6] http://www.choosemyplate.gov/food-groups/vegetables-why.html

"…fats that are liquid at room temperature, like the vegetable oils used in cooking. Oils come from many different plants and from fish. Oils are NOT a food group, but they provide essential nutrients. Therefore, oils are included in USDA food patterns."[7] Avocados, as well as some fish, nuts and olives, are listed as food-based sources of oils.

In summary, MyPlate provides no rationale for the exclusion of fruits and vegetables that fail to meet the 10% DV minimum nutrient content or "low-fat" criteria currently required under 21 C.F.R. § 101.75, and includes considerable information that all such foods be included.

3. National Heart Lung and Blood Institute

The National Cholesterol Education Program of the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) recommends dietary and other measures for the prevention of CHD. The scientific basis for these recommendations was most recently reported in the third edition of the Adult Treatment Panel (ATP III) (Grundy et al., 2004). This report recommends, three to five servings per day of fresh, frozen or canned vegetables without added fat, sauce or salt, and two to four servings per day of fresh, frozen, canned or dried fruits. The following rationale was provided for this recommendation.

> "…dietary patterns appear to influence baseline risk beyond the known risk. For example, populations that consume diets high in fruits, vegetables, whole grains, and fatty acids appear to be at a lower baseline risk than can be explained by standard risk factors. The particular nutrients that impart this lower risk have not been adequately defined, but strong candidates include antioxidant nutrients, folic acid, other B-vitamins, omega-3 fatty acids, and other micronutrients."

[7] http://www.choosemyplate.gov/food-groups/oils.html

ATP III devoted considerable attention to dietary and other lifestyle factors with the potential to affect the risk of CHD. It was concluded that restriction of total fat is not necessary for the management of lipid risk factors. The rational for this recommendation was as follows,

> "Among the fatty acids that make up the total fat in the diet, only saturated fatty acids and *trans* fatty acids raise LDL cholesterol levels [reference number deleted]. Thus, serum levels of LDL cholesterol are independent of intakes of total fat per se. ATP II advised limiting total fat in Step I and Step II diets to $\leq$30 percent of calories primarily as a means of achieving lower intakes of saturated fatty acids. The focus of the dietary approach to reducing CHD risk then and now is on dietary fatty acids that raise LDL cholesterol concentrations."

ATP III also provided evidence statements consistent with the recommendations noted above that replacement of saturated fatty acids with MUFA are beneficial for reduction of CHD risk. Specifically, the report stated,

> **"Evidence statements**: Monounsaturated fatty acids lower LDL cholesterol relative to saturated fatty acids. Monounsaturated fatty acids do not lower HDL cholesterol nor raise triglycerides.
>
> **Evidence statement:** Dietary patterns that are rich in monounsaturated fatty acids provided by plant sources and rich in fruits, vegetables, and whole grains and low in saturated fatty acids are associated with decreased CHD risk (C1). However, the benefits of replacement of saturated fatty acids with monounsaturated fatty acids has not been adequately tested in controlled clinical trials.
>
> **Recommendations:** Monounsaturated fatty acids are one form of unsaturated fatty acids that can replace saturated fatty acids. Intake of monounsaturated fatty acids can range up to 20 percent of total calories. Most monounsaturated fatty acids should be derived from vegetable sources, including plant oils and nuts."

In addition to the statements noted above, ATP III provided several sample menus of heart-healthy diets that included avocados as a component of a vegetable sandwich and a salad.

The ATP III report is currently under revision and ATP IV is expected in the near future. The scientific evidence reviewed in this petition, as well as that considered by other governmental and professional associations, suggests that ATP IV will make similar recommendations with respect to the effects of dietary fruits, vegetables and total fat on CHD risk. Nevertheless, until this report is issued, ATP III remains in effect.

In summary, the National Cholesterol Education Program, as described in ATP III, provides no rationale for the exclusion of fruits and vegetables that fail to meet the 10% DV minimum nutrient content or "low-fat" criteria currently required under 21 C.F.R. § 101.75, and considerable information that all such foods be included.

4. Institute of Medicine

The IOM report on Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (commonly referred to as the macronutrient report) (Institute of Medicine, 2002) did not make specific recommendations for the optimum intake of fruits and vegetables with respect to the risk of CHD. This report did note that the naturally occurring sugars in fruits should not count towards added sugars and that both fruits and vegetables are good sources of dietary fiber. However, because fruits and vegetables are not macronutrients, they were not a major focus of this report.

Recommendations for total fat and fatty acid classes did received considerable attention in the macronutrient report. As noted previously, the AMDR for total fat of 20-35% of energy was used in the 2010 *DGA* as a basis for not recommending a low-fat diet. Rather, the *DGA* state that unsaturated fats be substituted for saturated and *trans* fatty acids as part of a moderate fat diet. The main objective of the macronutrient report was the establishment of nutrient requirements rather than reduction of chronic disease risk *per se*. Nevertheless, the IOM elected not to recommend a lower fat diet due at least partially to the fact that moderate fat intake (within the AMDR) may be preferable to a lower fat diet for the risk of CHD. Specifically, the IOM observed,

> "Compared to higher fat intakes, low fat, high carbohydrate diets may modify the metabolic profile in ways that are considered to be unfavorable with respect to chronic diseases such as coronary heart disease (CHD) and diabetes…These changes include a reduction in high density lipoprotein cholesterol concentration, an increase in serum triacylglycerol concentration, and higher responses in postprandial glucose and insulin concentrations. This metabolic pattern has been associated with increased risk for CHD and type 2 diabetes in intervention and prospective studies [reference numbers deleted]. Although changes in the metabolic profile do occur, strong evidence that low fat diets actually predispose to either CHD or diabetes does not exist."

MUFA are not essential nutrients so the IOM did not establish an AMDR for these fatty acids in the macronutrient report. Nevertheless, this report made note of the potentially beneficial association between MUFA and risk of CHD.

> "Population data on monounsaturated fatty acid intake and risk of coronary heart disease (CHD) are limited. However, in long-term follow-up studies of the Seven Countries Study, higher intakes of monounsaturated fatty acids were associated with decreased rates of CHD mortality (Keys et al., 1986). Other reports indicate that monounsaturated fatty acids have a neutral or beneficial effect on risk (Hu et al., 1997; Kromhout and de Lezenne Coulander, 1984; Pietinen et al., 1997)."

In summary, the IOM macronutrient report (2002) provides no rationale for the exclusion of fruits and vegetables that fail to meet the 10% DV minimum nutrient content or "low-fat" criteria currently required under 21 C.F.R. § 101.75.

C. Professional organizations

Many professional organizations publish dietary recommendations designed to help consumers manage the risk of CHD and other chronic health-related conditions. No attempt was made to comprehensively identify such recommendations, but noteworthy examples are summarized below.

1. The American Heart Association

AHA's national goals for cardiovascular health promotion and disease reduction through the year 2020 have been published (Lloyd-Jones et al., 2010). The goal is, "By 2020, to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%."

Dietary recommendations were among those considered critically important to achieve the overall goal. Emphasis was given to dietary habits and behaviors with the strongest evidence base for a causal effect on CVD events (rather than risk factors), diabetes and/or obesity. Recommendations pertaining to beneficial dietary patterns rather than specific nutrients were emphasized, in part, because they can be more readily communicated to consumers, health professionals and policy makers and due to the challenges of measuring nutrient intakes in large populations

The first of five dietary goals considered as a necessary metric to monitor the success of achieving the 2020 goal states that at least 4.5 cups of fruits and vegetables should be consumed per day. The prominence of these foods in the DASH diet as well as their importance in weight management were noted in the scientific rationale for this recommendation. Increased consumption of fish and fiber-rich whole grains as well as reduced consumption of sodium and sugar-sweetened beverages were the remaining primary dietary metrics as a basis to monitor whether the population is adhering to a healthy eating pattern.

AHA also provides dietary information directly to consumers through a variety of sources including a website that describes the "Simple 7" heart health factors[8]. The first Simple 7 recommendation pertains to increased consumption of fruits and vegetables, "**Eat vegetables and fruits.** They are high in vitamins, minerals and fiber — and they're low in calories. Eating a variety of deeply colored fruits and vegetables may help you control your weight and your blood pressure." The remaining recommendations include increased consumption of fiber-rich whole grains and fish, reduced consumption of saturated and *trans* fats, cholesterol and added sugars as well as advice to savor new flavors.

A comprehensive discussion of the scientific basis for dietary recommendations from the AHA was published in 2006 (Lichtenstein et al.). An important component of these guidelines is to consume a wide variety of fruits and vegetables. The rationale for this recommendation is quoted below.

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[8] http://mylifecheck.heart.org/Multitab.aspx?NavID=10&CultureCode=en-US

"Consume a Diet Rich in Vegetables and Fruits
Most vegetables and fruits are rich in nutrients, low in calories, and high in fiber. Therefore, diets high in vegetables and fruits meet micronutrient, macronutrient, and fiber requirements without adding substantially to overall energy consumption. Whether it is the vegetables and fruits themselves or the absence of other foods displaced from the diet that is associated with CVD risk reduction has yet to be determined. Regardless, diets rich in vegetables and fruits have been shown to lower BP and improve other CVD risk factors in short-term randomized trials [reference number deleted]. In longitudinal observation studies, persons who regularly consume such diets are at a lower risk of developing CVD, particularly stroke."

This document also includes practical tips intended to help consumers implement the recommendations. Several such tips pertain to fruits and vegetables.

- Eat fresh, frozen, and canned vegetables and fruits without high-calorie sauces and added salt and sugars
- Replace high-calorie foods with fruits and vegetables
- Increase fiber intake by eating beans (legumes), whole-grain products, fruits and vegetables
- Encourage the consumption of whole vegetables and fruits in place of juices

These recommendations state, "A variety of vegetables and fruits are recommended. Vegetables and fruits that are deeply colored throughout (e.g., spinach, carrots, peaches, berries) should be emphasized because they tend to be higher in micronutrient content than are other vegetables and fruits such as potatoes and corn."

As noted in this petition, the AHA believes raw fruits and vegetables, as well as canned and frozen fruits and vegetables prepared without added fats and sugars, should qualify for the dietary saturated fat and cholesterol and risk of CHD health claim. The fruits and vegetables that would be affected by the proposed amendment that are "deeply colored throughout" are avocados, beets, some grapes, plums and sea buckthorn berries. AHA believes that sweet corn and other fruits and vegetables should also qualify for the dietary saturated fat and cholesterol and risk of CHD health claim because they may be beneficial and there is no scientific basis to exclude them. However, we continue to believe that consumers would benefit from additional variety in the fruits and vegetables they choose.

The AHA recommendations do not specify a recommended limit for total fat consumption. Rather, the focus of these recommendations is to limit the consumption of saturated and *trans* fats. Persons with metabolic syndrome are encouraged to avoid very low-fat diets if elevated triglycerides or depressed HDL-C concentrations are present; however, little emphasis on total fat is provided in the AHA guidelines.

The AHA also makes few recommendations pertaining to the use of unsaturated fatty acids. Efforts to lower saturated and *trans* fats by replacement of animal fats with PUFA and MUFA are recognized. In addition, the recommendations observe that some clinical trial data and/or prospective observational studies have demonstrated that replacement of saturated fatty acids with PUFA or MUFA may reduce the risk of CHD, but no specific recommendations are made with respect to these fatty acid classes.

In summary, the most recent diet and lifestyle recommendations from the AHA provide no rationale for the exclusion of fruits and vegetables that fail to meet the 10% DV minimum nutrient content or "low-fat" criteria currently required under 21 C.F.R. § 101.75, and considerable information that all such foods be included.

2. The Academy of Nutrition and Dietetics

The Academy of Nutrition and Dietetics (AND) (formerly the American Dietetic Association) does not have a position paper devoted exclusively to the promotion of increased consumption of fruits and vegetables. However, the Academy does support such efforts as part of compliance with dietary guidance from the U.S. government. A position statement entitled, "Total Diet Approach to Communicating Food and Nutrition Information," (Nitzke and Freeland-Graves, 2007) states the following.

> "Promote *variety, proportionality, moderation,* and *gradual improvement.* Variety refers to an eating pattern that includes foods from all MyPyramid food groups and subgroups. Proportionality, or balance, means eating more of some foods (fruits, vegetables, whole grains, fat-free or low-fat milk products), and less of others (foods high in saturated or *trans* fats, added sugars, cholesterol, salt, and alcohol)."

AND has a specific position statement pertaining to dietary fatty acids (Kris-Etherton et al., 2007). This statement supports the IOM AMDR for total fat of 20-35% of energy for total fat as well as recommendations from the *DGA* to replace saturated fats with *cis*-unsaturated fatty acids.

> "ADA and DC [Dietitians of Canada] concur with the acceptable macronutrient distribution range of the DRI report on macronutrients (12) for ALA, which is 0.6% to 1.2% of energy. The median intake of ALA in the United States and Canada is 0.5% energy. The intake of TFA should be reduced to as low as possible. SFA should be replaced with *cis* unsaturated fat or complex carbohydrates to maintain a total fat intake of 20% to 35% of energy. To a limited extent, SFA calories can be replaced with protein."

This position paper mentions avocados several times as a source of dietary MUFA.

In summary, the most recent position statements from the AND provide no rationale for the exclusion of fruits and vegetables that fail to meet the 10% DV minimum nutrient content or "low-fat" criteria currently required under 21 C.F.R. § 101.75, and some information that all such foods be included.

D. International organizations

Numerous countries have issued dietary guidelines that recommend increased consumption of fruits and vegetables and/or substitution of unsaturated fatty acids for their saturated counterparts. Such countries include Canada[9], France[10], the United Kingdom[11], Japan[12], China[13] and Australia[14].

A very comprehensive set of recommendations entitled, "Fats and fatty acids in human nutrition. Report of an expert consultation," was recently published by the FAO/WHO (2011). This report was not intended to address the overall diet, but a general statement recommended that fruits and vegetables be part of a predominant dietary pattern.

> "A general recommendation is to follow a dietary pattern predominantly based on whole foods (i.e., fruits and vegetables, whole grains, nuts, seeds, legumes, other dietary fibre sources, LCPUFA-rich seafood) with a relatively lower intake of energy dense processed and fried foods, and

[9] http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/myguide-monguide/index-eng.php
[10] http://www.the-food-guide-pyramid.com/frenchdiet.html
[11] http://www.nhs.uk/LiveWell/Goodfood/Pages/Goodfoodhome.aspx
[12] http://www.healthyeatingclub.org/info/articles/diet-guide/japan-dg.htm
[13] http://www.afic.org/healthytips.php?news_id=340&start=0&category_id=26&parent_id=26&arcyear=&arcmonth=
[14] http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/n31.pdf

> sugar-sweetened beverages; and to avoid consumption of large portion sizes."

This document concluded that there is "probable" evidence that total fat is unrelated to the risk of CHD and total cancer, and "insufficient" information to suggest that this macronutrient is associated with body weight/adiposity. For these, and other reasons, the panel supported the AMDR of 20-35% of total fat as recommended by the IOM (Institute of Medicine, 2002).

The panel also concluded that there is "convincing" evidence that replacement of MUFA and PUFA for saturated fatty acids lowers LDL-C concentrations and recommended an AMDR for total PUFA of 6-11 % en.

In summary, dietary recommendations and guidance from numerous countries, as well as a comprehensive review by an FAO/WHO consultation, provide no rationale for the exclusion of fruits and vegetables that fail to meet the 10% DV minimum nutrient content or "low-fat" criteria currently required under 21 C.F.R. § 101.75, and considerable information that all such foods be included.

In conclusion, AHA believes the absence of scientific information from the governmental, professional and international communities that certain fruits and vegetables be avoided on the basis of their micronutrient or fat content provides compelling support for the proposed amendment.

V. REGULATORY PRECEDENT

Numerous exceptions have been made by FDA to enforcement of the 10% minimum nutrient content and "low-fat" requirements for fruits and vegetables, as well as for other foods. AHA believes these exceptions illustrate the agency's intent to encourage consumption of these wholesome foods and provide ample regulatory precedent for the proposed amendment.

1. 10% DV minimum nutrient content requirement

FDA elected to exempt raw fruits and vegetables from the 10% DV minimum nutrient content requirement for the implied nutrient content claim "healthy." The agency provided the rational for this decision in the final rule for this claim (59 *Federal Register* 24232, 24244, May 10, 1994).

> "One comment stated that requiring a fruit or vegetable to meet the definition of 'good source' for any of the six nutrients mentioned above would eliminate cucumbers, grapes, green beans, and iceberg lettuce from bearing a 'healthy' claim. The comment argued that all fruits and vegetables that meet the proposed definition for 'healthy' should be allowed to use the term without having to meet any nutrient contribution requirement. The comment contended that fruits and vegetables are inherently healthy and are the only food group for which such a general statement can be made.
>
> After considering this comment, the agency is providing one narrow exception to the requirement that foods be a good source of one of the six nutrients of public health significance to qualify to bear a 'healthy' claim. Current dietary guidance emphasizes consumption of fruits and vegetables, and diets high in fruits and vegetables have been associated with various specific health benefits, including lower occurrence of coronary heart disease and some cancers ...
> Consistent with this guidance, FDA believes that increased consumption of raw fruits and vegetables can contribute significantly to a healthy diet and to achieving compliance with dietary guidelines, even if particular items, such as celery and cucumbers, do not contain 10

> percent of the daily value of one of the six nutrients of public health significance. Precluding such foods from being termed 'healthy' could confuse consumers and undermine an important element of current dietary guidance. FDA will therefore allow use of the term 'healthy' in connection with raw fruits and vegetables that do not meet the nutrient content requirement, if the other elements of the 'healthy' definition are met."

FDA later proposed to extend this exemption to single-ingredient frozen fruits and vegetables (61 *Federal Register* 5349, 5352, February 12, 1996) for the following rationale.

> "Because of the likelihood that most consumers are unaware of the exemption for raw fruits and vegetables, consumers will likely not recognize that there are alternative fruit and vegetable products that are precluded from bearing the claim but that are just as useful as raw fruits or vegetables in assisting consumers in meeting dietary goals. Furthermore, it was not the intent of the agency to suggest that the goal of increasing fruits and vegetables in the diet could only be achieved by consuming raw products, or that raw products are necessarily superior to all other fruit and vegetable products. FDA acknowledges that there are processed fruit and vegetable products, like frozen fruits and vegetables, that can be used to assist consumers in constructing a diet that is consistent with dietary recommendations; but those foods are currently ineligible to bear the 'healthy' claim because they do not meet the 10 percent nutrient contribution requirement."

Finally, FDA extended this exemption to canned fruits and vegetables composed solely of fruits and vegetables in the final rule for the "healthy" claim (62 *Federal Register* 14349, 14352, March 25, 1998) on the basis of data that demonstrated such products are nutritionally similar to raw and frozen fruits and vegetables. In addition, FDA stated,

> "Furthermore, the agency is concerned that an inappropriate message could be sent to consumers if a 'healthy' claim were permitted to appear on the raw or frozen version of the fruit or vegetable product but were precluded from appearing on the canned version. Such a situation might not only confuse consumers, it would also be inconsistent with the 1995 Dietary Guidelines. These guidelines state that 'the availability of fresh

> fruits and vegetables varies by season and region of the country, but frozen and canned vegetables ensure a plentiful supply of these healthful foods throughout the year.' The guidelines therefore recognize that canned as well as frozen fruits and vegetables can be used interchangeably in the diet with, and are just as helpful as, raw fruits and vegetables. Moreover, consumers should be informed that these foods serve as appropriate and useful alternatives to raw fruits and vegetables in assisting them in achieving their dietary goals."

FDA also noted that ingredients such as water, spices, flavors or other additives that do not change the level of macro or micronutrients in the food can be utilized under this exemption. However, ingredients such as added sugars and fats are not permitted (62 *Federal Register* 14349 at 14353).

AHA agrees with all of these decisions and the rationale behind them. We also believe there is no logical basis why such reasoning should not be applied to similar products for the purpose of making health claims. Therefore, our proposed new subparagraphs to 21 C.F.R. § 101.75(c)(2)(ii) use the same wording that the agency employed in 21 C.F.R. § 101.65(d)(2)(i).

Furthermore, FDA proposed to exempt such fruits and vegetables from the 10% DV minimum nutrient content requirement for all health claims in its response to petitions from the National Food Processors Association and the American Bakers Association (60 *Federal Register* 66206, 66213, December 21, 1995).

> "Although the agency has not been persuaded that elimination of the 10 percent nutrient contribution requirement is in order, or that it should permit fortification so that a food could qualify to bear a health claim, the agency has been persuaded by the arguments raised in the petitions that it should act to modify the 10 percent nutrient contribution requirement. As

stated above, the agency acknowledges that the 10 percent nutrient contribution requirement has had the unintended effect of precluding some foods that contribute to a healthful diet, and whose consumption is encouraged by the dietary guidelines, from bearing health claims. As discussed above, the agency's primary goals in establishing the 10 percent nutrient contribution requirement were to preclude foods of little or no nutritional value from bearing health claims and, at the same time, to enhance the likelihood of consumers constructing overall daily diets that conform to current dietary guidelines.

FDA recognizes that precluding certain fruits, vegetables, and grain products from bearing health claims because of the 10 percent nutrient contribution requirement is contrary to that goal. The agency agrees with the arguments raised in the petitions that certain fruits, vegetables, and grain products that otherwise meet the requirements of the specific health claim should be able to bear the claim even though they do not contain 10 percent of one of the six listed nutrients because these foods comprise a major part of a balanced and healthful diet, and because current dietary guidance promotes consumption of these foods. Moreover, diets high in fruits, vegetables, and grain products have been associated with various specific health benefits, including lower occurrence of coronary heart disease and of some cancers [reference numbers deleted] and therefore, are exactly the types of foods that should be included in the diet to reduce the risk of specific diet-related diseases. Precluding such foods from bearing health claims could confuse consumers and undermine the utility of health claims.

Furthermore, the foods described in the petitions are not the types of foods FDA intended to preclude from bearing health claims when it established the 10 percent nutrient contribution requirement. In fact, these foods can contribute significantly to a balanced and healthful diet and to achieving compliance with dietary guidelines even though they do not meet the 10 percent nutrient contribution requirement. Consequently, the agency tentatively concludes that fruit and vegetable products comprised solely of fruits and vegetables, enriched grain products that conform to a standard of identity, and bread that conforms to the standard of identity for enriched bread except that it contains whole wheat or other grain products not permitted under that standard, that do not meet the 10 percent nutrient contribution requirement but that meet all other aspects of the health claim should be permitted to bear a health claim."

FDA has not finalized this proposed rule; however, the agency has granted exemptions to the 10% DV minimum nutrient content requirement for health claims on multiple occasions.

Such a request for salad dressings to bear the sterol/stanol ester claim was granted (65 *Federal Register* 54686, 54711, September 8, 2000). A major consideration in this decision was that salad dressings promote the consumption of vegetables.

> "The agency concludes that, with respect to dressings for salad, the minimum nutrient content requirements of §101.14(e)(6), while important, are outweighed by the public health importance of communicating the cholesterol-lowering benefits from consumption of plant sterol/stanol esters. The agency believes that the value of health claims will not be trivialized or compromised by their use on dressings for salad because dressings for salad often are consumed with foods rich in nutrients and fiber. Salads, for example, are usually rich in vegetables that provide important nutrients at significant levels, e.g., tomatoes—vitamins A and C; carrots—vitamin A; spinach—vitamin A and calcium.

FDA has granted similar exemptions for walnuts to bear the qualified health claim (QHC) for reduced risk of CHD for its own claim[15] as well as part of the tree nut QHC[16]. In addition, the agency has provided exemptions from this requirement for olive[17], canola[18] and corn[19] oils as well as salad dressings and shortenings made from these oils for their respective CHD-related QHCs.

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[15] http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm072910.htm
[16] http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm072926.htm
[17] http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm072963.htm
[18] http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm072958.htm
[19] http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm072956.htm

AHA agrees strongly with all of the opinions and decisions made by FDA in this area. The exemption from 21 C.F.R § 101.14(e)(6) for the "healthy" claim of the same fruits and vegetables that would be affected by the proposed amendment, as well as the agency's proposal to exempt such foods from the same requirement for all health claims, are particularly compelling. Furthermore, the exemption of vegetable oils that contain virtually no micronutrients other than vitamin E from this requirement gives additional credence to the exemption of fruits and vegetables that often provide an array of micronutrients. AHA knows of no rational reason why the same reasoning should not be applied to the fruits and vegetables that would be affected by the proposed amendment.

B. "Low-fat" requirement

As noted above, evolving scientific evidence has shown that the type of fat in the diet is more important for the maintenance of optimum health than the amount of fat. This evolution has prompted the *DGA*, the AHA and other professional organizations to recommend diets that are moderate, rather than low, in total fat.

FDA's position on this topic has also changed from an emphasis on low- to moderate-fat diets. Specifically, the agency initially proposed that foods eligible to make the soy and risk of CHD health claim be required to be low in fat, but eliminated this requirement because total fat intake is not directly related to CHD and because the inherent fat content of soybeans would have prevented many products made from whole beans from making the claim (64 *Federal Register* 57700, 57717, October 26, 1999). The agency also chose not to impose a "low-fat" criterion on products eligible to make the sterol/stanol ester health claim because fat is the only vehicle capable of delivering these cardioprotective substances, which were deemed to have public health significance (65 *Federal Register* 54686, 54708, September 8, 2000). FDA also noted that this policy was consistent with the fifth edition of the *DGA*, which recommends "moderate" rather than "low" fat diets. The agency also permitted foods with moderate fat content (less than 6.5 g total fat per reference amount customarily consumed [RACC]) to bear the whole grain foods and risk of CHD health claim authorized under the Food and Drug Administration Modernization Act[20]. In addition, the agency has allowed a QHC for nut-containing products that are low in saturated fat and cholesterol, but not necessarily low in total fat[21]. Finally, FDA has extended this position to the QHCs for olive oil[22], canola oil[23], and corn oil[24]. The agency's wording for olive oil was,

> "…FDA concurs with current dietary guidelines that consuming diets low in saturated fat and cholesterol is more important in reducing CHD risk than consuming diets low in total fat. Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that olive oil, vegetable oil spreads, dressings for salads, shortenings, and olive oil-containing foods that bear a MUFAs from olive oil and CHD qualified health claim meet the 'low fat' criterion."

In addition to the precedent FDA has established for granting exemptions from the "low-fat" criterion for health claims, the agency has also granted such exemptions from the total fat disqualifier level. Such exemptions go well beyond those for low fat because

20 http://www.fda.gov/Food/LabelingNutrition/LabelClaims/FDAModernizationActFDAMAClaims/ucm073634.htm

21 http://www.cfsan.fda.gov/~dms/qhcnuts2.html .

22 http://www.cfsan.fda.gov/~dms/qhcolive.html .

23 http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm072958.htm

24 http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm072956.htm

products with more than 13 g fat per RACC (rather than 3 g) are permitted to bear health claims.

Such an exemption was granted for products making the sterol/stanol ester health claim. The agency cited four criteria it considered in making this decision (65 *Federal Register* 54686 at 54709). These criteria were: whether the disease in question is of public health significance, whether the absence of an exemption from the disqualifier level would severely limit the number of foods that would qualify to bear the claim; whether there is evidence that the population to which the health claim is targeted is not at risk for the disease; and whether there are other public health reasons for granting the exemption. FDA concluded that sterol/stanol ester-containing foods should be granted the requested exemption because CHD is a significant public health concern, because lack of an exemption would severely limit the foods that would qualify for the claim, and because sterol/stanol ester-containing products have a significant potential to benefit public health by virtue of the fact that they can lower serum T-C and LDL-C without adversely affecting HDL-C. The agency also justified the exemption by concluding that "…current scientific evidence does not indicate that diets high in unsaturated fat are associated with CHD…" and cited the 2000 *DGA* that states, "Choose a diet that is low in saturated fat and cholesterol and **moderate in total fat**" (emphasis provided).

In addition, FDA granted exemptions to the total fat disqualifier for the QHCs for olive oil[25], canola oil[26], and corn oil[27] in addition to not requiring eligible foods to be low in

[25] http://www.cfsan.fda.gov/~dms/qhcolive.html .
[26] http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm072958.htm

fat, as described above, as long as they bear the disclosure statement, "See nutrition information for total fat content" placed immediately adjacent to and directly beneath the claim, with no intervening material, in the same size, typeface, and contrast as the claim itself as required by 21 CFR § 101.13(h).

AHA agrees strongly with all of the opinions and decisions made by FDA in this area and believes strongly that they provide a compelling precedent for the proposed amendment.

VI. BENEFICIAL EFFECTS OF THE AHA HEART-CHECK PROGRAM

As noted previously, approval of the proposed amendment will allow additional fruits and vegetables to bear the AHA Heart-Check symbol. Data collected by AHA have shown that this symbol is trusted by consumers and increases the sales of foods (including vegetables) for which it is used.

Data from a 2009 survey conducted by the AHA [28] showed that this organization and the U.S. government were those most trusted by consumers to decide whether a food product should be eligible to bear a health symbol (see Table 1).

Data from a 2010 survey conducted by Health Focus International available from the AHA[29] show that of a group of commonly seen label and package symbols, the AHA Heart-Check symbol is the most influential with consumers (see Table 2).

[27] http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm072956.htm
[28] http://www.heart.org/idc/groups/heart-public/@wcm/@private/@fc/documents/downloadable/ucm_300869.pdf
[29] Available from Dennis Milne: e-mail dennis.milne@heart.org

Table 1
Which organizations would you trust to decide if a product's packaging may display health symbols or messages

Not sure	12%
Group of food industry representatives	6
Product manufacturer	7
Consumer advocate organization	26
Independent panel of scientists/nutritionists	38
Government	58
American Diabetes Association	59
American Heart Association	73

The Heart-Check symbol also has a positive effect on sales of products; especially when Heart-Check certified products are promoted. A market research study conducted by the AHA in 2009[30] in collaboration with Catalina Marketing found that sales of a group of certified products increased by 2.4% during a four-week baseline period compared to a 7.4% increase during a four-week period of additional in-store promotion using the

Table 2
When shopping how much does the following label, seal or mark influence your choice? (strong/moderate)

Company health cue	17%
Kosher (Parve) certified	17%
Suitable for vegetarians	19%
Glycemic index	26%
Certified organic	39%
Heart symbol	58%
Whole grain stamp	62%
American Heart Association	66%

Heart-Check symbol. In addition, 85% of consumers reported that they found this symbol "helpful" or "very helpful," 75% reported that it improved their likelihood to buy,

[30] http://www.heart.org/idc/groups/heart-public/@wcm/@private/@fc/documents/downloadable/ucm_300868.pdf

and 60% stated that it positively influenced their purchasing decision when compared with products that did not bear the symbol.

Use of the symbol has also been shown to increase the sales of fresh and canned vegetables. A controlled study conducted by AHA in 2010[31] in collaboration with Catalina Marketing examined the effect of fruits and vegetables (among other products) on sales among four U.S. consumer segments based on interest in nutrition. The consumer segments were defined as:

- Heart of Gold – high interest in nutrition, read and understand the nutrition facts panel
- Healthy Alternatives – high interest in nutrition but from the perspective of natural and organic as a primary driver
- Healthy Convenience – moderate to low interest in nutrition, high focus on convenience
- Conflicted Heart – moderate to low interest in nutrition, do not understand how to read/use the nutrition facts panel, struggle with adopting or maintaining a healthy dietary pattern

Baseline sales of products were monitored at 65 test and 65 control grocery stores in South Carolina, upstate New York as well as metro New York and Philadelphia for a 52-week period. Products eligible to bear the AHA Heart-Check logo in the test stores were then promoted for four weeks with shelf tags displaying the logo. No such promotion

[31] Available from Dennis Milne: e-mail dennis.milne@heart.org

occurred in the control stores. Results of the study for fruits and vegetables are presented in Table 3.

Table 3
Change in sales (test vs. control stores) of fresh and canned vegetables among four nutrition-oriented consumer segments after promotion with the AHA Heart-Check symbol

Category	Conflicted Heart	Healthy Convenience	Healthy Alternatives	Heart of Gold
Canned vegetables	6.5%[a]	NS	9.3%[a]	7.0%
Fresh vegetables	36.2%[b]	36.9%[b]	16.2%[b]	15.8%[b]

[a] $p<0.20$
[b] $p<0.10$

In summary, the AHA Heart-Check program is well regarded by a broad array of U.S. consumers and has been shown to increase the sales of eligible products including canned and fresh vegetables. AHA believes the ability to extend this program to virtually all raw fruits and vegetables, as well as select processed forms of these foods, will increase its appeal to the fruit and vegetable industry and increase the sales and consumption of these highly recommended and beneficial foods.

VII. ENVIRONMENTAL IMPACT ASSESSMENT

AHA chooses to avail itself of the categorical exclusion with respect to an environmental impact assessment provided by 21 C.F.R. § 25.32(p). Accordingly, an environmental impact assessment is not required for this submission.

VIII. CONCLUSION AND CERTIFICATION

CHD (and more broadly CVD) continues to be an enormous public health concern in the U.S. AHA believes increased consumption of fruits and vegetables should be encouraged by all possible means to help address this concern. Approval of the proposed amendment to the dietary saturated fat and cholesterol and risk of CHD health claim would enable more of these foods to bear this claim and to become eligible for the AHA Heart-Check symbol. The scientific evidence presented in this document supports the proposed amendment. This evidence clearly shows that fruits and vegetables, as a group, have many nutritional benefits and are associated with reduced risk of CHD (and more broadly with CVD). In addition, controlled feeding studies confirm that increased intake of fruits and vegetables, as a group, favorably affect FDA-accepted CHD-related biomarkers. No scientific evidence was found to suggest that the fruits and vegetables that do not meet the "low-fat" definition or those that fail to meet the 10% DV minimum nutrient content requirement for health claims should be excluded from this claim because they compromise the hypocholesterolemic effect of diet low in saturated fat and cholesterol. In fact, evidence suggests that some such vegetables (e.g., avocados) may be cardioprotective in their own right. In addition to the supportive scientific evidence, ubiquitous recommendations from governmental and professional organizations (including the *DGA*) have been published to encourage consumption of fruits and vegetables as a group. FDA has consistently supported this philosophy in its proposals and rulemakings since enactment of the Nutrition Labeling and Education Act. This regulatory activity establishes a clear precedent for the proposed amendment. Finally, approval of this proposal will enable broader promotion of fruits and vegetable through the AHA Heart-Check symbol, which has been shown to increase sales. For these reasons, the AHA respectfully requests that FDA act as quickly as possible to issue an interim final rule tentatively authorizing this important amendment.

I hereby certify that, to the best of my knowledge, this petition is a representative and balanced submission that includes unfavorable information as well as favorable information known to me to be pertinent to the evaluation of the proposed qualified health claim.

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