



March 3, 2021

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Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
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Attn: Docket ID: FDA-2019-Q-0806

Dear Dr. Balentine:

We are writing on behalf of our client Barry Callebaut pertaining to above referenced Qualified Health Claim (QHC) petition entitled, "Petition for the Authorization of a Qualified Health Claim for Cocoa Flavanols and Reduced Risk of Cardiovascular Heart Disease" (Petition) submitted by Barry Callebaut AG (the petitioner).

On February 2, 2021, we supplemented our Petition with a recently published meta-analysis published by Krittanawong et al (Krittanawong) entitled: *Association between chocolate consumption and risk of coronary artery disease: a systematic review and meta-analysis*.¹ We supported the supplemental petition with cited references, however, we received feedback from the agency that the Krittanawong article describes specific studies that went into the meta-analysis in Figure 1 of the article and those studies were inadvertently not included in the reference list or the supplemental petition.

The agency has requested that in order to appropriately review the meta-analysis of Krittanawong it would be helpful to provide a further supplemental petition with copies of the Krittanawong meta-analysis and the six studies specifically evaluated in the analysis. Attached to this further supplemental petition we have provided the Krittanawong meta-analysis and its supplemental material that contains supplementary tables and data for the analysis.

¹ Association between chocolate consumption and risk of coronary artery disease: a systematic review and meta-analysis European Journal of Preventive Cardiology 0(0) 1–3! The European Society of Cardiology 2020 Krittanawong et al.

We have also attached (Appendix S 2.0) the six studies as included in the meta-analysis as noted in Figure 1 of Krittanawong; these studies are as follows: Greenberg 2018², Ho 2018³, Larsson 2018⁴, Lewis 2010⁵, Janszky 2009⁶, and Mink 2007⁷. These attached references were utilized by the study's authors to conduct their meta-analysis in support of their findings.

The study authors undertook this meta-analysis reasoning as follows:

“Clinical trials have shown that the consumption of chocolate has favorable effects on blood pressure and endothelial function.⁸ The previous meta-analysis showed that many dietary components, including chocolate, appear to be beneficial for cardiovascular disease.⁹ However, the potential benefit of increased chocolate consumption, reducing coronary artery disease (CAD) risk is not known. We aimed to explore the association between chocolate consumption and CAD.

II. Scope of Study

In their meta-analysis the study's authors “identified six prospective studies with a median follow-up of 8.78 years. The study population was composed of 336,289 individuals with 21,777 diseases. This was composed of 14,043 cases of CAD, 4,667 myocardial infarctions, 2735 cerebrovascular accidents and 332 cases of heart failure. Study subjects included 266,264 individuals from the United States, 68,809 from Sweden and 1216 from Australia. Compared with the consumption of not less than one time per week, higher chocolate consumption (>1 time per week or >3.5 times per month) was associated with a decreased risk of CAD.¹⁰”

² Greenberg, J.A. et al. Chocolate Intake and Heart Disease and Stroke in the Women's Health Initiative: a Prospective Analysis. *AM J Clin Nutr* 2018;108:41-48

³ Ho, Y. et al. Abstract 15879: Chocolate Consumption and Risk of Coronary Artery Disease, The Million Veteran Program. *Lifestyle and Behavioral Medicine*, 2018

⁴ Larsson, S. et al. Chocolate Consumption and Risk of Myocardial Infarction: a Prospective Study and Meta-Analysis. *Coronary Artery Disease*. 2016: 102: 1017-1022

⁵ Lewis, J. et al. Habitual Chocolate Intake and Vascular Disease: A Prospective Study of Clinical Outcomes in Older Women. *Arch Intern Med*

⁶ Janszky, I. et al. Chocolate Consumption and Mortality Following a First Acute Myocardial Infarction: The Stockholm Heart Epidemiology Program. *Journal of Internal Medicine*. 2009

⁷ Mink, P. Flavonoid Intake and Cardiovascular Disease Mortality: A Prospective Study in Postmenopausal Women. *Am J Clin Nutr*; 85: 895-909

⁸ Balzer J, Rassaf T, Heiss C, et al. Sustained benefits in vascular function through flavanol-containing cocoa in medicated diabetic patients a double-masked, randomized, controlled trial. *J Am Coll Cardiol* 2008; 51: 2141–2149.

⁹ Kwok CS, Gulati M, Michos ED, et al. Dietary components and risk of cardiovascular disease and all-cause mortality: a review of evidence from meta-analyses. *Eur J Prev Cardiol* 2019; 26: 1415–1429.

¹⁰ Association between chocolate consumption and risk of coronary artery disease: a systematic review and meta-analysis *European Journal of Preventive Cardiology* 0(0) 1–3! The European Society of Cardiology 2020 Krittanawong et al

III. Findings

A. As a result of their meta-analysis, the authors found “that chocolate consumption (>1 time per week or >3.5 times per month) is associated with a reduced risk of CAD. Similar to their prior findings in a previous meta-analysis that showed that chocolate consumption was associated with a decreased risk of CAD.¹¹ The authors stated that “there was substantial heterogeneity in that meta-analysis due to adjusted variables in included studies and the comparison was between the highest and lowest intake of chocolate. In their most recent study, the authors performed sensitivity analyses to determine whether the results remained the same as follows: “[f]or example, after excluding Greenberg et al., which used a cut-off of more than 3.5 times per month, chocolate consumption more than once per week remained associated with a decreased risk of CAD. The authors also performed sensitivity analyses by excluding Ho et al. (Ho), because the results were presented as an abstract. After excluding Ho., the study authors concluded that chocolate consumption more than one time per week or more than 3.5 times per month is probably associated with a decreased risk of CAD¹².”

B. The study authors surmised that chocolate consumption may offer cardio protective effects due to several nutrients. The authors stated that “flavanols (e.g. epicatechin, cat-echin and procyanidins) have been shown to reduce myocardial infarct size in one animal study, to reduce platelet aggregation and improve endothelial function in several randomized controlled trials of healthy individuals or people with CAD.^{13,14} Methylxanthines have been shown to have beneficial effects on cardiovascular function.¹⁵ Polyphenols have been shown to facilitate nitric oxide synthesis.^{16,17} Finally, stearic acid has also been shown to reduce mean platelet volume.”¹⁸ The authors concluded that “[o]verall, the benefits of nutrients in chocolate appear promising and chocolate consumption at least once a week may be beneficial for CAD prevention.” The study authors noted that, one study

¹¹ Yan S, Li X, Jin Y and Lu J. Chocolate consumption and risk of coronary heart disease, stroke, and diabetes; a meta-analysis of prospective studies. *Nutrients* 2017; 9: 688.

¹² Krittanwong Ibid

¹³ Rull G, Mohd-Zain ZN, Shiel J, et al. Effects of high flavanol dark chocolate on cardiovascular function and platelet aggregation. *Vasc Pharmacol* 2015; 71: 70–78.

¹⁴ Schroeter H, Heiss C, Balzer J, et al. (–)-Epicatechin mediates beneficial effects of flavanol-rich cocoa on vascular function in humans. *Proc Natl Acad Sci USA* 2006; 103: 1024–1029.

¹⁵ Sansone R, Ottaviani JJ, Rodriguez-Mateos A, et al. Methylxanthines enhance the effects of cocoa flavanols on cardiovascular function: randomized, double-masked controlled studies. *Am J Clin Nutr* 2017; 105: 352–360.

¹⁶ Schini-Kerth VB, Auger C, Kim JH, et al. Nutritional improvement of the endothelial control of vascular tone by polyphenols: role of NO and EDHF. *Pflugers Arch: Eur J Physiol* 2010; 459: 853–862.

¹⁷ Karim M, McCormick K and Kappagoda CT. Effects of cocoa extracts on endothelium-dependent relaxation. *J Nutr* 2000; 130: 2105s–2108s.

¹⁸ Kelly FD, Sinclair AJ, Mann NJ, et al. A stearic acid-rich diet improves thrombogenic and atherogenic risk factor profiles in healthy males. *Eur J Clin Nutr* 2001; 55: 88–96.

showed a negative correlation between lower Syntax scores and larger amounts of chocolate consumed.¹⁹ The authors reasoned that the unfavorable effects of supplemental calories (e.g. fats, milk, or sugar) from chocolate products commercially available need to be taken into account. Further long-term, double-blind, randomized controlled trials are needed to determine the underlying physiological mechanisms of the cardio-protective effects of chocolate and the association with CAD risk. It was suggested by the authors that dark chocolate consumption at least once a week (e.g. as a substitute for sugared candy) with overall caloric intake tracking is probably safe.

The authors acknowledged certain limitations to this study. First, they noted that there may be dietary confounders in those observational studies. For example, fats, milk, or sugar in chocolate, total energy intake, body mass index and types of chocolate products (milk, dark, or white) could confound any potential association observed. The authors also alluded to the caloric intake of commonly available chocolate products. The authors suggested that generalization and the external validity of their findings were perhaps hampered by the geographical origins of the included studies, as they were mainly conducted in Europe and the United States. Finally, they found that lifestyle factors (e.g., exercise, physical activity) were not adjusted for in the multivariate models of the original studies.

As to the expressed concern about the increased caloric intake associated with “fats, milk, or sugar in chocolate, total energy intake, body mass index and types of chocolate products (milk, dark, or white) could confound any potential association observed,”²⁰ thereby potentially outweighing the benefits of the cocoa flavanols (CFs). The petitioner respectfully suggests that in its prior Supplemental Petition filed on, August 30, 2019, it noted that its Petition addressed the problem of high caloric intake associated with common chocolate products. The benefits of high flavanol cocoa products that are produced utilizing improved processing techniques that significantly increases the level of CFs, without the risk of high caloric intake.

The petitioner attached to the prior Supplemental Petition (August 30, 2019), a study conducted entitled: *Survey of Commercially Available Chocolate and Cocoa-Containing Products in the United States Comparison of Flavan-3-ol Content with Nonfat Cocoa Solids, Total Polyphenols, and Percent Cacao* (Miller et. al., Journal of Agricultural and Food Chemistry, September 15, 2009). This survey examined a broad range of chocolate and cocoa-containing products to determine flavanol content. The chocolates included in this survey include Hershey’s Special Dark, Lindt Excellence (70% Cocoa) and Dove Promises Dark Chocolate. These surveyed products on average contained 1.785 mg/g of CFs (See table 3, DC-1, DC-2 and DC-3, column DP 10.)

¹⁹ Martins Duarte H, Rocha de Oliverira MC, Jun R, et al Association between chocolate consumption and severity of first infarction. *Int J Cardiovasc Sci* 2019; 32; 576-582.

²⁰ Krittanwong Ibid

As a comparison, the Petitioner's high flavanol dark chocolate contains on average 22 mg/g (CFs), which is at least 10 times higher in flavanol content than typical available dark chocolate. As an example, it would take about 112 grams of typical dark chocolate having approximately 550 calories to deliver 200mg of CFs, while it would only take about 10 grams of high flavanol dark chocolate having approximately 50 calories to deliver the suggested proposed daily requirement of 200mg CFs.

We respectfully submit that the suggested limitations noted by the study authors of increased caloric intake caused by "fats, milk, or sugar in chocolate," are addressed by the special processing of cocoa allowing for a significant increase in the content of CFs in "high flavanol" cocoa and "high flavanol" semi-sweet chocolate as shown in the Petition on pages 161 and 162 (reproduced below).

"In order to make it possible to consume moderate amounts of cocoa powder or semi-sweet/dark chocolate, optimized processing techniques have been developed that allow the manufacturing of cocoa powder and semi-sweet/dark chocolates preserving the high amounts of CFs that are naturally present in the cocoa bean. This development has opened up the possibility to deliver the effective dose of CFs (≥ 200 mg) contained in a relatively small amount of cocoa powder or semi-sweet/dark chocolate, such as to restrict the intake of high-caloric, low flavanol containing products that would otherwise jeopardize a balanced diet and facilitate weight gain. At least 200 mg of CFs can be provided by:

Daily consumption of at least 200 mg CFs, contained in either 2.5g high-flavanol cocoa powder or 10g semi-sweet/dark chocolate, as well as in applications thereof, can easily be consumed in the context of a balanced diet." (Petitioner's Petition Pages 161 and 162).

IV. CONCLUSIONS

The study authors found in their meta-analysis that chocolate has beneficial cardiovascular systems stating that "[i]n conclusion, our analysis suggests that the consumption of chocolates at least once a week is associated with a reduction in the risk of CAD."²¹

We agree with authors' findings as to the benefit of chocolate in reducing the risk of CAD. We strongly believe that providing consumers with information regarding this beneficial effect would allow consumers to make informed decisions on chocolate products that may contribute to their overall cardiac health, as set forth in our Petition and further supported by this recent study of CF. In addition to these well-documented beneficial effects, additional data supports that

²¹ Krittanwong Ibid

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CFs also reduce blood pressure; especially in pre-hypertensive and moderately hypertensive individuals. Educating the consumer to the benefits of the consumption of nutritionally-appropriate CF-containing foods has a real potential to positively improve public health. We therefore respectfully ask the agency to consider these additional studies and comments and respectfully urge the agency to authorize the proposed claims.

Respectfully submitted,

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Enclosures

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