U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY & APPLIED NUTRITION

JAN 3 1 2020

Melvin S. Drozen
Evangelia C. Pelonis
Keller and Heckman LLP
1001 G Street, N.W., Suite 500 West
Washington, D.C. 20001

Re: Docket Number FDA-2019-P-1911

Dear Mr. Drozen and Ms. Pelonis:

This responds to your citizen petition dated April 19, 2019, requesting that the Food and Drug Administration (FDA or we) "amend the definition of 'dietary fiber' at 21 C.F.R. § 101.9(c)(6)(i) by adding 'Acacia (gum arabic)'…to the existing list of isolated or synthetic non-digestible carbohydrates determined by [FDA] to have physiological effects that are beneficial to human health."[1] See Citizen Petition from Melvin S. Drozen and Evangelia C. Pelonis, Keller and Heckman LLP, on behalf of Nexira, Ingredion Incorporated and TIC Gums, Alland & Robert, and Importers Service Corporation, submitted to the Division of Dockets Management, Food and Drug Administration, dated April 19, 2019 ("Petition"), at page 1.

In the *Federal Register* of May 27, 2016, we published a final rule entitled, "Food Labeling: Revision of the Nutrition and Supplement Facts Labels" (81 FR 33742). The final rule, among other things, defines dietary fiber as "non-digestible soluble and insoluble carbohydrates (with 3 or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health" (see 21 CFR 101.9(c)(6)(i)). In the final rule, we identified seven isolated or synthetic non-digestible carbohydrates that have a physiological effect that is beneficial to human health. We also stated that any interested person may seek to amend the listing of added fibers through the existing citizen petition process in 21 CFR 10.30.[2]

[1] Similar to the language used in the petition, we will refer to 'Acacia (gum arabic)' as 'gum acacia' throughout this response.
[2] For up-to-date information on the additional non-digestible carbohydrates that FDA has determined may be added to the definition of dietary fiber, see "Questions and Answers on Dietary Fiber," available at http://www.fda.gov/food/food-labeling-nutrition/questions-and-answers-dietary-fiber#synthetic_fibers.

U.S. Food and Drug Administration
Center for Food Safety & Applied Nutrition
5001 Campus Drive
College Park, MD 20740
www.fda.gov

In accordance with 21 CFR 10.30(e)(3), we are denying your petition. This letter sets out the basis for our determination that the strength of the evidence is not sufficient to demonstrate that the consumption of gum acacia has a physiological effect that is beneficial to human health.

I. FDA's Consideration of the Scientific Evidence

Your petition requests that FDA add gum acacia to the list of dietary fibers in 21 CFR 101.9(c)(6)(i) on the grounds that gum acacia "has beneficial physiological effects on (1) postprandial blood glucose and insulin levels and (2) energy intake and satiety" (Petition at page 2).

In the *Federal Register* of March 2, 2018 (83 FR 8997), we announced the availability of a final guidance document entitled, "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30)" ("final guidance"). This final guidance describes our views on the scientific evidence needed, and the approach for evaluating the scientific evidence, on the physiological effects of isolated or synthetic non-digestible carbohydrates added to foods that are beneficial to human health. It also discusses the inclusion of studies on diseased populations under certain circumstances as part of our evaluation of the totality of the scientific evidence, provides detail on the physiological endpoints that we consider when reviewing the scientific evidence, and provides detail regarding factors we consider when evaluating the strength of the evidence. We reviewed your petition using the factors identified in the final guidance.

Postprandial Blood Glucose and/or Insulin

The petition states that "consumption of [gum acacia] facilitates the beneficial effect of postprandial blood glucose and/or insulin levels" (Petition at page 10).

The petition identifies nine studies[3,4] that evaluated the effect of gum acacia consumption on postprandial blood glucose and insulin. Scientific conclusions could not be drawn from five

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[3] Akeo K, Kojima M, Uzuhashi Y. Physiological function of gum Arabic. *Food Chemicals Monthly* 2002; 6:85-89; Campbell JM, Fahey GC, Demichele SJ et al. Metabolic characteristics of healthy adult males as affected by ingestion of a liquid nutritional formula containing fish oil, oligosaccharides, gum Arabic and antioxidant vitamins. *Food and Chemical Toxicology* 1997; 35:1165-1176; Larson R, Nelson C, Wang Q et al. The effects of gum acacia on satiety, glycemic response and gastrointestinal tolerance. April 2019, *unpublished*; Nasir O, Babiker S, Salim AM. Protective effect of gum Arabic supplementation for type 2 diabetes mellitus and its complications. *International Journal of Multidisciplinary and Current Research* 2016; 4:288-294; Pouteau E, Ferchaud-Roucher V, Zair Y et al. Acetogenic fibers reduce fasting glucose turnover but not peripheral insulin resistance in metabolic syndrome patients. *Clinical Nutrition* 2010; 29:801-807; Ross AH, Eastwood MA, Brydon WG et al. A study of the effects of a dietary gum arabic in humans. *American Journal of Clinical Nutrition* 1983; 37:368-375; Sharma RD. Hypoglycemic effect of gum acacia in healthy human subjects. *Nutrition Research* 1985; 5:1437-1441; Torres N, Palacios-Gonzalez B, Noriega-Lopez L et al. Glycaemic index, insulinemic index and glycaemic load of soy beverages with a low and high content of carbohydrates. *Revista de Investigacion Clinica [Clinical Research Journal]* 2006; 58:487-497; Wolever T, Jenkins AL, Ezatagha A. Effect of dietary fiber incorporated into pudding on postprandial glucose and insulin responses. March 2019, *unpublished*.

[4] Your petition also identifies an additional 2004 unpublished Australian study that you submitted to FDA on February 13, 2017. While we reviewed this study when examining the materials you submitted as part of your

studies because of the following[5]: (1) no control group or an inappropriate control group was used (Nasir et al., 2016; Ross et al., 1983); (2) a mixture of non-digestible carbohydrates, including gum acacia, was used, and therefore the physiological effect of gum acacia could not be independently evaluated (Campbell et al., 1997; Pouteau et al., 2010); or (3) the study measured the glycemic index of gum acacia rather than postprandial blood glucose, and nutrient composition of the treatment and control beverages (e.g., amount of available carbohydrate and ingredients) was not provided (Torres et al., 2006).

Accordingly, the four human intervention studies from which we did draw conclusions are as follows.

Sharma (1985)

Twelve healthy men participated in a randomized cross-over design study[6] in which they consumed a glucose solution without gum acacia (control) or a glucose solution containing 20 grams (g) of gum acacia. The study subjects' postprandial blood glucose and postprandial insulin was measured at several intervals for 150 minutes after consumption of the glucose solutions. Consumption of the glucose solution containing gum acacia statistically significantly reduced postprandial glucose and postprandial insulin, as measured by area-under-the-curve (AUC),[7] compared to the control glucose solution ($P < 0.05$). However, there were no statistically significant differences in peak postprandial blood glucose or peak postprandial insulin after consumption of a glucose solution containing gum acacia versus the control glucose solution ($P > 0.05$).

Akeo et al. (2002)

Twelve healthy men participated in a cross-over design study[8] in which they consumed a sucrose solution without gum acacia (control) or a sucrose solution containing either 5 g or 10 g of gum acacia. The study subjects' postprandial blood glucose was measured at several intervals for 150 minutes after consumption of the sucrose solutions. The peak postprandial blood glucose was statistically significantly lower with the consumption of both sucrose solutions containing gum acacia (5 g, 10 g) compared to the control sucrose solution ($P < 0.05$ for both). No statistical analysis comparing the two doses was reported in the study. The postprandial blood glucose, as measured by AUC, was also not reported. Postprandial insulin was not measured.

Larson et al. (2019; *unpublished*)

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petition, the study was not considered as part of our scientific evaluation of this petition nor addressed in this response because it is not publicly available.

[5] This section contains the studies from which scientific conclusions could not be drawn. Such studies may have other flaws in addition to those specifically mentioned.

[6] The article provides no description as to whether the study was randomized or double-blinded (where neither the participants nor the experimenters know who is receiving a particular treatment).

[7] The rise and fall of blood glucose over several hours after consuming a food, beverage, or meal is often reported as area-under-the-curve (AUC) (sometimes referred to as incremental AUC).

[8] The article provides no description as to whether the study was randomized or double-blinded (where neither the participants nor the experimenters know who is receiving a particular treatment).

Forty-eight healthy men and women participated in a randomized, double-blind, cross-over design study in which they consumed orange juice without gum acacia (control) or orange juice with either 20 g or 40 g of gum acacia added. The orange juice (8 oz) was given to subjects as part of a breakfast meal that included a bagel and cream cheese. The study subjects' postprandial blood glucose was measured at several intervals for 240 minutes after consumption of the breakfast meal. There was a statistically significant difference in peak postprandial blood glucose between the orange juice containing 20 g of gum acacia and the control orange juice ($P < 0.05$). However, the peak postprandial blood glucose with the orange juice containing 40 g of gum acacia did not reach statistical significance when compared to the control orange juice ($P > 0.05$). No statistically significant differences were observed in the postprandial blood glucose, as measured by AUC, between the orange juice containing either 20 g or 40 g of gum acacia and the control orange juice ($P > 0.05$ for both). No dose-response effect was observed between the two doses of gum acacia ($P > 0.05$). Postprandial insulin was not reported in this study.

Wolever et al. (2019; *unpublished*)

Forty healthy men and women participated in a randomized, double-blind, cross-over design study in which they consumed pudding without gum acacia (control) or pudding containing either 13 g or 24 g of gum acacia. All pudding contained 59 g of digestible (available) carbohydrates. The study subjects' postprandial blood glucose and insulin were measured at several intervals for 120 minutes after consumption of the pudding. No statistically significant differences were observed in postprandial blood glucose, as measured by AUC or peak, between the pudding containing gum acacia (13 g or 24 g) and the control pudding ($P > 0.05$ for both). However, consumption of the pudding containing 13 g of gum acacia statistically significantly lowered postprandial insulin, as measured by both AUC and peak ($P < 0.05$). Consumption of the pudding containing the higher dose (24 g) of gum acacia statistically significantly lowered postprandial insulin, as measured by AUC, compared to the control pudding ($P < 0.05$). However, peak concentration of postprandial insulin was not statistically significantly different between the pudding containing 24 g of gum acacia and the control pudding ($P > 0.05$). Furthermore, the lower dose of gum acacia (13 g) showed a statistically significantly higher reduction (20%) on peak concentration of postprandial insulin as compared to the reduction achieved (9%) with the higher dose (24 g) ($P < 0.05$).

Energy Intake

Your petition states that "consumption of [gum acacia] facilitates the beneficial effect of energy intake reduction and increased satiety" (Petition at page 16).

We identified seven publications[9] which included seven studies[10] that evaluated the effect of gum acacia consumption on energy intake. Scientific conclusions could not be drawn from five publications because of one or more of the following: (1) there was no control group (Nasir et al., 2016); (2) a mixture of non-digestible carbohydrates, including gum acacia, was used and therefore, the physiological effect of gum acacia could not be independently evaluated (Davidson et al., 1998); (3) no statistical analysis was done comparing the treatment and control groups (Babiker et al., 2012, 2017, 2018); and/or (4) study subjects were asked to consume or keep records of their usual daily diet, but the studies did not provide any information on dietary and energy intake and/or physical activity for assessing the effect of gum acacia on body mass index and/or body fat percentage, and therefore it is unclear whether any changes in outcomes were attributable to gum acacia consumption or other changes in the subjects' diet or activity that may have affected body weight/composition (Babiker et al., 2012, 2017, 2018; Nasir et al., 2016).

Accordingly, the three human intervention studies from which we did draw conclusions are as follows.

Calame et al. (2011)

This publication included two randomized, double-blind, cross-over studies.

Study 1

The first study evaluated the effect of three different doses, and two different brands, of gum acacia on energy intake and subjective scores of satiety. Twelve healthy men were assigned to drink water (250 mL) containing 0 g (control), 10 g, 20 g, or 40 g of gum acacia from two different brands after eating a standard breakfast. Energy intake was measured three hours after the consumption of a standard breakfast and Visual Analog Scale (VAS) scores of satiety[11] (i.e.,

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[9] Babiker R, Merghani TH, Elmusharaf K et al. Effects of gum Arabic ingestion on body mass index and body fat percentage in healthy adult females: two-arm randomized, placebo controlled, double-blind trial. *Nutrition Journal* 2012; 11:1-7; Babiker R, Elmusharaf K, Keogh MB et al. Metabolic effects of gum Arabic (Acacia Senegal) in patients with type 2 diabetes mellitus (T2DM): randomized, placebo controlled double blind trial. *Functional Foods in Health and Disease* 2017; 7:219-231; Babiker R, Elmusharaf K, Keogh MB et al. Effect of gum Arabic (Acacia Senegal) supplementation on visceral adiposity index (VAI) and blood pressure in patients with type 2 diabetes mellitus as indicators of cardiovascular disease (CVD): a randomized and placebo-controlled clinical trial. *Lipids in Health and Disease* 2018; 17:1-8; Calame W, Thomassen F, Hull S et al. Evaluation of satiety enhancement, including compensation, by blends of gum Arabic. A methodological approach. *Appetite* 2011; 57:358-364; Davidson MH, Dugan LD, Stocki J et al. A low-viscosity soluble-fiber fruit juice supplements fails to lower cholesterol in hypercholesterolemic men and women. *Journal of Nutrition* 1998; 128:1927-1932; Larson R, Nelson C, Wang Q et al. The effects of gum acacia on satiety, glycemic response and gastrointestinal tolerance. April 2019, *unpublished*; Nasir O, Babiker S, Salim AM. Protective effect of gum Arabic supplementation for type 2 diabetes mellitus and its complications. *International Journal of Multidisciplinary and Current Research* 2016; 4:288-294.

[10] Findings from one study were reported in two publications (Babiker et al., 2017, 2018), and findings from two studies were reported in one publication (Calame et al., 2011).

[11] Satiety is often measured using VAS scores that subjectively measure various endpoints, such as hunger, appetite, and feelings of fullness. We intend to consider subjective measures of satiety (a state of "fullness") to understand the mechanism by which a potential reduction in energy intake from food might occur with the consumption of an isolated or synthetic non-digestible carbohydrate (U.S. Food and Drug Administration, "Scientific Evaluation of the

the difference between the VAS scores measured at the start of the study subtracted from those scores per time interval per person) were recorded every 30 minutes after the subjects had consumed the different gum acacia doses. Compared to the control, energy intake was statistically significantly lower (100 to 200 kcal) when 40 g of gum acacia was consumed ($P <$ 0.05). Energy intake was not statistically significantly different for the 10 and 20 g doses of gum acacia compared to the control ($P > 0.05$ for both). There was a statistically significant increase in the VAS scores, with respect to the subjective perception of satiety, between the various doses of gum acacia (10 g, 20 g, 40 g), compared with the control, over the study's three-hour time interval ($P < 0.05$ for all).

Study 2

The second study, which involved 58 men and women, was designed to identify a minimum dose (5 or 10 g) of gum acacia to have an effect on satiety. Subjects drank a glass of water (250 mL) containing 0 g (control), 5 g, or 10 g of gum acacia after eating a standard breakfast. Three hours later, an *ad libitum* meal of pasta with tomato and cheese sauce was offered. Subjects were instructed to eat their meal until they felt comfortably full, after which, subjects drank a second glass of water (250 mL) containing 0 g (control), 5 g, or 10 g of gum acacia. Three hours later, a second *ad libitum* meal of macaroni and cheese was offered to the study subjects. A statistically significant decrease in energy intake (approximately 60 kcal) during consumption of the first *ad libitum* meal was observed for the two doses of gum acacia compared to control ($P < 0.05$ for both). No statistically significant differences in energy intake during consumption of the second *ad libitum* meal were observed for the two doses of gum acacia compared to control ($P > 0.05$ for both). Both doses of gum acacia statistically significantly increased the overall VAS score for satiety ($P < 0.05$ for both).

Larson et al. (2019; *unpublished*)

Forty-eight healthy men and women participated in a randomized, double-blind, cross-over design study in which energy intake was measured and appetite was rated after consumption of orange juice (8 oz) with either 0 g (control), 20 g (low dose), or 40 g (high dose) of gum acacia. The orange juice was given to subjects as part of a breakfast meal, which included one plain bagel and one-ounce cream cheese. At 240 minutes, an *ad libitum* cheese pizza was offered to the study subjects to eat until they were comfortably full. The pizza was weighed before and after consumption to measure energy intake. There were no statistically significant differences in energy intake from the consumption of pizza between either the low dose (741 ± 230 kcal) or high dose (737 ± 245 kcal) of gum acacia compared with the control (756 ± 274 kcal) ($P > 0.05$ for both).[12] No statistically significant differences were observed in 24-hour food intake after consumption of the breakfast meal ($P > 0.05$ for both doses).

Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as Citizen Petition (21 CFR 10.30) (February 2018)." Available at https://www.fda.gov/media/101183/download).

[12] Appetite, sensations of hunger, fullness, and desire to eat were assessed by VAS at 15, 30, 45, 60, 90, 120, 180, and 240 minutes after baseline. Among the eight time points (per dose) assessed for the subjective measures of satiety, only two time points showed statistically significant differences – after 15 minutes (hunger, satisfaction, and fullness) and after 240 minutes (hunger) – when consuming a breakfast with orange juice containing 40 g of gum acacia compared to breakfast with the control orange juice ($P < 0.05$ for both). There were no statistically

II. Strength of the Scientific Evidence

We evaluated the strength of the scientific evidence by considering various factors, such as the number of studies and sample sizes of each study, dose response data if available, the types of foods tested, the relevance of the body of scientific evidence to the U.S. population or target subgroup, and the overall consistency of the total body of evidence. Based on this evidence, we evaluated whether the findings presented in the relevant clinical studies demonstrated that there is a beneficial physiological effect of gum acacia consumption to human health, and therefore, whether to propose to include gum acacia as a dietary fiber in the dietary fiber definition.

Postprandial Blood Glucose and/or Insulin

There were four publicly available studies (Akeo et al., 2002; Larson et al., 2019 *unpublished*; Sharma, 1985; Wolever et al., 2019 *unpublished*) from which scientific conclusions could be drawn for the effect of gum acacia consumption on postprandial blood glucose and/or insulin. Two studies (Akeo et al., 2002; Sharma, 1985), each conducted in 12 healthy men, evaluated three dose comparisons (5 g, 10 g, 20 g) of gum acacia when added to a glucose solution beverage. There were statistically significant lowering effects on postprandial blood glucose when gum acacia was consumed at 5 g, 10 g, and 20 g in a glucose solution beverage. The two most recent studies (Larson et al., 2019 *unpublished*; Wolever et al., 2019 *unpublished*), with four dose comparisons, evaluated the effect of gum acacia when consumed with food. Both studies included a larger sample size (n = 40, 48) than prior studies, and doses of gum acacia ranged from 13 g to 40 g. The results from these two studies were mixed. One study (Wolever et al., 2019 *unpublished*) showed no statistically significant effect on either AUC or peak blood glucose when subjects consumed pudding containing gum acacia (13 g or 24 g). In another study (Larson et al., 2019 *unpublished*), gum acacia (20 g or 40 g) was added to a beverage (orange juice) as part of a breakfast meal. No statistically significant effects on either AUC or peak postprandial blood glucose were observed when 40 g of gum acacia was consumed. With consumption of the 20 g dose of gum acacia, there was a statistically significant lowering effect on peak postprandial blood glucose but not AUC. There was no dose-response effect observed in the study.

We evaluated the data on the relationship between postprandial blood glucose and postprandial insulin. Only two studies (Sharma, 1985; Wolever et al., 2019 *unpublished*) reported the effect of gum acacia consumption (20 g, and 13 g and 24 g, respectively) on both postprandial blood glucose and postprandial insulin. There was a statistically significant effect of lowering AUC postprandial insulin with gum acacia consumption at the three doses. Gum acacia consumption at the 13 g dose, but not at the 20 g or 24 g doses, had a statistically significant lowering effect on peak postprandial insulin. However, only one dose (20 g) demonstrated a statistically significant lowering effect on AUC postprandial blood glucose. The other two doses (13 g to 24 g) reported no statistically significant effect on either AUC or peak postprandial blood glucose.

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significant differences in the appetite ratings at any time point when the orange juice containing the low dose (20 g) of gum acacia was consumed ($P > 0.05$ for all).

In summary, for postprandial glucose, a statistically significant effect of gum acacia was mostly observed in smaller studies where gum acacia was added to a sugar solution beverage. In larger studies where gum acacia was consumed with food, a statistically significant effect was not observed, except for one dose (13 g, the smallest dose out of four doses) which showed a lowering of peak postprandial blood glucose concentration. For postprandial insulin, there is limited data to base our decision (i.e., two studies – one of which added gum acacia to a sugar solution beverage – with three dose comparisons[13]), which weakens our confidence in the relationship between gum acacia and postprandial insulin. Furthermore, in the one study that measured a dose response effect of gum acacia on postprandial insulin, the lower dose of gum acacia showed a statistically significantly higher reduction in peak concentration compared to the higher dose. Due to the limited evidence, with a small number of dose comparisons, it is not possible to explain the inconsistencies in the findings of the effect of gum acacia on postprandial blood glucose and postprandial insulin. We considered whether there was a plausible explanation for the inconsistencies in the studies. We were unable to find a plausible explanation for the inconsistency in the findings or to consider those studies that did not find a statistically significant effect as being less relevant to or less important in determining the strength of the total body of evidence. Consequently, we have determined that the strength of the scientific evidence does not support a finding of a beneficial effect of gum acacia consumption on postprandial blood glucose and/or insulin.

Energy Intake

There were three publicly available studies (Calame et al., 2011 *Study 1*; Calame et al., 2011 *Study 2*; Larson et al., 2019 *unpublished*) for which scientific conclusions could be drawn for the effect of gum acacia on energy intake. One study (n = 12) showed a statistically significant beneficial effect of 40 g of gum acacia on energy intake (100 to 200 kcal reduction), but no statistically significant effect was observed when 10 g and 20 g of gum acacia were consumed (Calame et al., 2011 *Study 1*). A second study (n = 58) reported a statistically significant beneficial effect of gum acacia at doses of 5 g and 10 g on energy intake (60 kcal reduction) (Calame et al., 2011 *Study 2*). A third study (n = 48) reported no statistically significant effect of gum acacia at doses of either 20 g or 40 g on energy intake (Larson et al., 2019 *unpublished*). Furthermore, no statistically significant differences were observed in the subject's 24-hour food intake after consumption of gum acacia. Due to the limited evidence, it is not possible to explain the inconsistencies in the findings. We considered whether there was a plausible explanation for the inconsistencies between studies that found a statistically significant effect and studies that found no statistically significant effect. We were unable to find a plausible explanation for the inconsistency in the findings or to consider those studies that did not find a statistically significant effect as being less relevant to or less important in determining the strength of the total body of evidence. Consequently, we have determined that the strength of the scientific evidence does not support a finding of a beneficial effect of gum acacia consumption on energy intake.

III. Conclusion

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[13] Sharma, 1985 and Wolever et al., 2019 *unpublished*, reported the effects of gum acacia consumption (20 g, and 13g and 24 g respectively) on both postprandial blood glucose and postprandial insulin.

Based on our consideration of the scientific evidence and other information submitted with the petition, and other pertinent scientific evidence and information, we conclude that the strength of the evidence is insufficient to demonstrate that the consumption of gum acacia has a physiological effect that is beneficial to human health. Consequently, we do not plan to propose to amend the list of nondigestible carbohydrates that meet the definition of dietary fiber to include gum acacia as a dietary fiber based on this scientific evidence. Therefore, in accordance with 21 CFR 10.30(e)(3), we are denying your petition.

We recognize, of course, that new scientific information may become available that demonstrates a beneficial physiological effect associated with the consumption of gum acacia. Although we are denying your petition, we would consider a new petition from you concerning the consumption of gum acacia that is based on new scientific information.

Sincerely,

Claudine Kavanaugh

Claudine Kavanaugh, Ph.D., MPH, RD
Director
Office of Nutrition
and Food Labeling
Center for Food Safety
and Applied Nutrition