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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): Guidance for Industry

Draft Guidance

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For questions regarding this draft document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1200.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

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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): Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance listed on the title page.

I. Introduction

This guidance document explains FDA's current thinking on information needed when submitting a citizen petition and the scientific review approach we plan to use for evaluating scientific evidence to determine whether an isolated or synthetic non-digestible carbohydrate that is added to food has a physiological effect that is beneficial to human health. The purpose of this guidance is to provide information to those submitting evidence to us to determine if the added non-digestible carbohydrate meets the definition of dietary fiber in our regulations for nutrition labeling of food for declaring the amount of dietary fiber on the Nutrition and Supplement Facts labels.

This guidance document addresses our current thinking for: (1) identifying published scientific articles that evaluate a physiological effect of an added non-digestible carbohydrate; (2) evaluating those studies from which scientific conclusions can be drawn; and (3) evaluating the strength of scientific evidence to determine whether there is a physiological effect that is beneficial to human health of an isolated or synthetic non-digestible carbohydrate that is added to foods.

[1] This guidance has been prepared by the Office of Nutrition and Food Labeling in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

Before 2016, FDA regulations did not define the term "dietary fiber." In the *Federal Register* of May 27, 2016 (81 FR 33742), we published a final rule amending our Nutrition and Supplement Facts label regulations (hereafter referred to as "the final rule"). 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. The final rule also identifies seven isolated or synthetic non-digestible carbohydrates that we have determined have beneficial effects for human health (21 CFR 101.9 (c)(6)(i)).

We derived our definition of dietary fiber from a 2002 Institute of Medicine (IOM) report that defines dietary fiber as non-digestible carbohydrates and lignin that are intrinsic and intact in plants. The IOM report also defines the term "functional fiber" as isolated, non-digestible carbohydrates that have beneficial physiological effects in humans. Functional fibers include synthetic non-digestible carbohydrates or isolated or extracted non-digestible carbohydrates that are produced using chemical, enzymatic, or aqueous processes. Finally, the IOM report defines the term "total fiber" as the sum of dietary fiber and functional fiber (IOM, 2002). We concluded in the final rule that label declarations of dietary fiber should accurately reflect the total amount of fiber present in a food that provides a physiological effect that is beneficial to human health to assist consumers in maintaining healthy dietary practices.

This guidance does not address non-digestible carbohydrates that are intrinsic and intact in plant-based foods. These intrinsic and intact fibers by their very nature meet the definition of "dietary fiber" in the final rule. Plant-based foods that contain non-digestible carbohydrates that are intrinsic and intact and that are typically consumed as part of the U.S. diet include fruits, vegetables, whole grains[2], legumes, and nuts (IOM, 2001). These fiber-containing foods have been shown to provide health benefits (Dietary Guidelines for Americans, 2015; 21 CFR 101.77). They also contain other food

[2] Grains and grain products made from the grain seed (e.g., kernel or oat groat).

components, such as vitamins and minerals, which may be associated with beneficial physiological effects.

The non-digestible carbohydrates present in fiber-containing foods that are produced using mechanical processes, (e.g., milling), such that the product is still considered a food that contains other nutrients normally found in the foods are also considered to be intrinsic and intact (IOM, 2002). These intrinsic and intact fibers by their very nature also meet the definition of "dietary fiber" in the final rule. These products include cereal bran, cocoa powder, flours, vegetable purees or pomace, vegetable protein extracts, parts of a food (e.g., outer coat of peas), and non-digestible carbohydrates (e.g., resistant starch) that are created during the normal processing of food (e.g., flaked corn cereal). Accordingly, these types of foods are not affected by this guidance.

Foods or parts of foods that have been processed, resulting in a product with an increased concentration of non-digestible carbohydrates and that no longer contain or contain lower amounts of food components, such as vitamins and minerals, are not considered to be intact and intrinsic. Non-digestible carbohydrates that are obtained from non-food sources, such as stems, branches, and trunks of trees, inedible hulls and husks, seaweed, and fungus, also are not considered to be intact and intrinsic. For purposes of this guidance, FDA refers to these fibers interchangeably as isolated or synthetic non-digestible carbohydrates or added non-digestible carbohydrates.

An isolated or synthetic non-digestible carbohydrate can only be declared as a dietary fiber on the Nutrition and Supplement Facts label if FDA determines it has physiological effects beneficial to human health and is listed in our regulations in 21 CFR 101.9(c)(6)(i). Any interested person may ask us to amend our regulations to list a new isolated or synthetic non-digestible carbohydrate as a dietary fiber by submitting a citizen petition (as provided in 21 CFR 10.30) or, if the added non-digestible carbohydrate is the subject of an authorized health claim using the health claim petition process in 21 CFR 101.70,[3] FDA would consider it to meet the definition of dietary fiber and would amend the definition accordingly.

III. Scientific Evaluation of the Beneficial Physiological Effects of Isolated or Synthetic Non-digestible Carbohydrates

Our scientific evaluation process will involve a series of steps to: (1) assess scientific studies and other data; (2) eliminate those from which no conclusions about the

[3] Guidance to Industry is already available for the scientific review of health claims (FDA, 2009). This guidance document describes the process by which we will evaluate scientific evidence to determine whether an isolated or synthetic non-digestible carbohydrate has a physiological effect that is beneficial to human health and therefore meets the dietary fiber definition.

physiological effects of an added non-digestible carbohydrate can be drawn; and (3) evaluate the strength of the scientific evidence to determine whether the carbohydrate provides a physiological effect that is beneficial to human health.

A. Identifying Published Studies That Evaluate a Beneficial Physiological Effect to Human Health

We will consider the publicly available data and written information primarily from intervention studies regarding the beneficial physiological effects of added non-digestible carbohydrates. We will review intervention studies that are submitted to us in citizen petitions (21 CFR 10.30) requesting the addition of specific added non-digestible carbohydrates to the list of dietary fibers that we already have determined have a beneficial physiological effect to human health and therefore which may be included in the amount of dietary fiber declared on Nutrition and Supplement Facts labels. Interested parties should submit all publicly available human studies on a specific isolated or synthetic non-digestible carbohydrate as part of a citizen petition, regardless of the studies' findings. We may identify additional relevant intervention studies through a literature search. We intend to focus our review primarily on articles reporting human intervention studies because these studies are available and can provide evidence from which scientific conclusions can be drawn about the beneficial physiological effect of a specific isolated or synthetic non-digestible carbohydrate in humans. Observational studies on the physiological benefits of isolated or synthetic non-digestible carbohydrates, for example, are not available because food composition databases currently do not provide the content of these types of carbohydrates in food. Therefore, it is not possible to assess intake data for added non-digestible carbohydrates in an observational study.

In evaluating the available scientific evidence, we will first separate relevant articles on human intervention studies from other types of data and information, for example, review articles and meta-analyses.

- Intervention Studies

In an intervention study, subjects are provided the added non-digestible carbohydrate of interest (intervention group), typically either added to a conventional food or dietary supplement. The quality and quantity of the added non-digestible carbohydrate should be controlled for. In randomized controlled trials, subjects are assigned to an intervention group by chance rather than systematically. Individual subjects may not be similar to each other, but the intervention and control groups should be similar after randomization. Randomized controlled trials offer the best assessment of a causal relationship between a non-digestible carbohydrate and a physiological effect because they control for known confounders of results (i.e., other factors that could affect the physiological endpoint). Through random assignment of subjects to the intervention and control groups, these

studies avoid selection bias, that is, the possibility that those subjects most likely to have a favorable outcome, independent of an intervention, are preferentially selected to receive the intervention. Potential bias also is reduced by "blinding" the study so that the subjects do not know whether they are receiving the intervention, or by "double blinding," in which neither the subjects nor the researchers who assesses the outcome knows who is in the intervention group and who is in the control group. By controlling the test environment, including the amount and composition of non-digestible carbohydrate consumed and all other dietary factors, these studies also can minimize the effects of variables or confounders on the results.[4] Therefore, randomized, controlled intervention studies provide the strongest evidence of whether there is a relationship between an added non-digestible carbohydrate and a physiological effect (Greer et al., 2000).

Such studies also can provide convincing evidence of a cause and effect relationship between an intervention and an outcome (Kraemer et al., 2005). Randomization, however, may result in unequal distribution of the characteristics of the subjects between the control and treatment groups (e.g., blood [serum or plasma] low-density lipoprotein (LDL) cholesterol levels are significantly different). If the baseline values are significantly different, then it is difficult to determine if differences at the end of the study were due to the intervention or to differences present at the beginning of the study. When the non-digestible carbohydrate of interest is provided as a dietary supplement, a placebo should be provided to the control group. When the substance is a food, it may not be possible to provide a placebo and therefore subjects in such a study may not be blinded. Although the study may not be blinded in this case, a control group is still needed to draw conclusions from the study.

Randomized controlled trials typically have either a parallel or cross-over design. Parallel design studies involve two groups of subjects, the test group and the control group, which simultaneously receive the added non-digestible carbohydrate or serve as the control. In a cross-over design study, all subjects cross over from the intervention group to the control group, and vice versa, after a defined time period.

Although intervention studies are the most reliable category of studies for determining a cause-and-effect relationship, generalizing from the studies conducted on selected populations to different populations may not be scientifically valid.

- Observational Studies

Observational studies can be designed to measure associations between food components

[4] Confounders are factors that are associated with both the physiological benefit in question and the intervention, and that if not controlled for, prevent an investigator from being able to conclude that an outcome was caused by an intervention.

and physiological and health-related endpoints. Observational studies lack the controlled setting of intervention studies. Observational studies are most reflective of free-living[5] populations and may be able to establish an association between a food component, such as an added non-digestible carbohydrate, and a beneficial physiological effect. Unlike intervention studies, observational studies cannot be used to determine whether an observed association establishes that the food component caused a change in the physiological or health-related endpoint or is a coincidence; that is, observational studies do not establish causation (Sempos et al., 1999). Observational studies generally rely on a dietary intake assessment method to estimate food intake. The nutrient content of reported foods is usually determined using some form of food composition database. While there are limitations in evaluating the association between a food component and a physiological or health-related endpoint (FDA, 2007), if information on the amount of an ingredient added to a food (e.g., an isolated or synthetic non-digestible carbohydrate) is available, information from observational studies could be considered. Food composition databases, however, currently do not provide the content of individual types of isolated or synthetic non-digestible carbohydrates in foods. Therefore, observational studies that rely on intake data for evaluating the association between an isolated or synthetic non-digestible carbohydrate and a physiological benefit are not available. If such observational studies become available, we will consider them.

- Research Synthesis Studies

Reports that discuss a number of different studies, such as review articles, which summarize the findings of individual studies, do not provide enough information on the individual studies for us to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on the individual studies prevents us from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. We need to be able to review the critical elements of each study to determine whether any scientific conclusions can be drawn from it. Therefore, we intend to use review articles and similar publications[6] only to identify reports of additional studies that may be useful to our scientific review and as background about the beneficial physiological effect of added non-digestible carbohydrates. If we identify additional studies this way, we intend to evaluate them individually. Most meta-analyses[7] also lack detailed information on the individual studies subject to the analysis. Therefore, we will only use them to identify reports of additional studies that may be useful to our scientific reviews and as background about the beneficial physiological effect of added non-digestible carbohydrates.

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[5] Free-living populations represent those who consume diets and have lifestyles (e.g., smoking, drinking, and exercise) of their own choice.

[6] Examples of "similar publications" include book chapters, abstracts, letters, and committee reports.

[7] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

- Animal and *in vitro* Studies

We intend to use animal and *in vitro* studies as background information regarding mechanisms that might be involved in any physiological effect of an isolated or synthetic non-digestible carbohydrate. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (IOM, 2005). Animal and *in vitro* studies can be used to generate hypotheses, investigate biological plausibility of hypotheses, or to explore a mechanism of action of a specific food component through controlled animal diets. However, these studies do not provide information from which scientific conclusions can be drawn regarding the beneficial physiological effects in humans of a food component, such as added non-digestible carbohydrates.

B. Evaluating Human Intervention Studies

Once we have identified the relevant human intervention studies, we will evaluate each study to determine whether any scientific conclusions can be drawn regarding the beneficial physiological effect of an added non-digestible carbohydrate. Critical elements of a study, such as design, data collection, and data analysis, may be so flawed that they make it impossible to draw scientific conclusions from the study. We do not intend to use studies from which we cannot draw any scientific conclusions about the beneficial physiological effect, and we will eliminate such studies from further review.

The following are examples of questions that we intend to consider when evaluating whether scientific conclusions can be drawn from an intervention study about the beneficial physiological effect of an isolated or synthetic non-digestible carbohydrate.

- *Have the studies specified and measured the isolated or synthetic non-digestible carbohydrate?*

The added non-digestible carbohydrate of interest should be provided in its isolated form, rather than in a naturally-occurring form in food. The added non-digestible carbohydrate also should not be added in combination with other non-digestible carbohydrates or other food components that may affect the physiological endpoint being measured. When a mixture of non-digestible carbohydrates is added to foods, scientific conclusions cannot be drawn about the role of the individual added non-digestible carbohydrate of interest.

- *Have the studies appropriately specified and measured a physiological endpoint that has a demonstrated beneficial physiological effect?*

There are a number of beneficial physiological effects associated with the consumption of dietary fibers, such as attenuation of blood glucose and cholesterol concentration and improved laxation (i.e., the elimination of fecal waste) (IOM, 2001). It is important that the physiological effect from consuming an isolated or synthetic non-digestible carbohydrate be associated with a specific physiological endpoint that has been shown to have a beneficial physiological effect to human health.

Attenuation of blood glucose levels can be measured in more than one way. Fasting blood glucose levels provide information on the long-term effects of a dietary intervention. Post-prandial blood glucose levels[8] provide information on the glycemic response over several hours after consuming a food, beverage, or meal. The rise and fall of blood glucose over several hours after consuming a food, beverage, or meal is often measured as the area-under-the-curve (AUC), rather than as a single data point fixed in time. Glycemic index[9] is not an appropriate measure for evaluating the effect of an isolated or synthetic non-digestible carbohydrate on attenuation of blood glucose. Glycemic index does not provide information on how an isolated or synthetic non-digestible carbohydrate affects the glycemic response of a food or beverage that contains nutrients (e.g., starch) that affect blood glucose levels.

Recognized measures of improved laxation (elimination of fecal waste) include reduced transit time of food through the intestinal tract and increased rates of defecation (e.g., stools per day) (Topping, 2007). Data on ease of defecation and reduced complaint of defecation is also considered a measure of improved laxation. While intake of an added non-digestible carbohydrate can increase fecal or stool weight, an increase in fecal weight does not necessarily indicate improved bowel function (i.e., laxation) (IOM, 2002). We intend to consider fecal/stool weight data in our reviews, but only to evaluate how changes in stool weight, as a result of the consumption of an isolated or synthetic non-digestible carbohydrate, is associated with changes in laxation.

Reduced energy intake from food consumption also is considered a physiological benefit. While not a physiological benefit itself, we intend to consider information regarding changes in satiety in our reviews to understand the mechanism by which a potential reduction in energy intake from food might occur with the consumption of an isolated or

[8] Post-prandial glucose measures the rise and fall of blood glucose after consuming a meal which reflects the intestinal absorption and clearance of glucose from the blood.

[9] Glycemic index measures the increase in blood glucose during the two hours after ingestion of a set amount of carbohydrate in a test food, compared to the same amount of carbohydrate from a reference food (white bread or glucose solution) measured in the same individual and under the same conditions, using the initial blood glucose concentration as a baseline.

synthetic non-digestible carbohydrate. Satiety is often measured using a Visual Analogue Scale that measures various endpoints such as hunger, appetite, and feelings of fullness.

Fermentation and changes in the microbiota in the large intestine are considered to be processes, rather than beneficial physiological effects. While physiological effects that are beneficial to human health may be an outcome of fermentation or changes in the colonic microbiota, we do not consider either to be valid and measurable predictors of these effects in humans.

- *Were the study subjects healthy or did they have a disease associated with the physiological effect being studied?*

Declarations made on Nutrition Facts labels are intended for the general healthy population. We will consider evidence from studies with subjects who have a disease that is associated with the physiological effect of interest only if extrapolating to individuals who do not have the disease is scientifically appropriate. Therefore, we intend to consider evidence from studies of subjects who have a disease only if the available scientific evidence demonstrates that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the added non-digestible carbohydrate affects these mechanisms in the same way in both diseased and healthy people. If such evidence is not available, we cannot draw any scientific conclusions from studies with subjects that have a disease that is associated with the physiological endpoint (e.g., improved laxation in individuals with chronic constipation). Therefore, we do not intend to use these types of studies to evaluate physiological benefits. However, we would consider studies that include individuals at risk of developing a disease (e.g., elevated LDL cholesterol levels, metabolic syndrome, or abnormal glucose tolerance test) or who have an unrelated disease (e.g., individuals with osteoporosis and being evaluated for attenuation of blood glucose levels).

- *Did the study include an appropriate control group?*

An appropriate control group represents study subjects who did not receive or consumed a lower amount of the added non-digestible carbohydrate of interest. All other aspects of the study design (e.g., duration) for the control and intervention groups should be similar. If an appropriate control group was not used, it is impossible to ascertain whether changes in the endpoint of interest were due to the added non-digestible carbohydrate or to unrelated and uncontrolled extraneous factors (Spilker, 1991; National Research Council, 2011). Without an appropriate control group, scientific conclusions cannot be drawn about a beneficial physiological effect of an added non-digestible carbohydrate. Therefore, we do not intend to use these types of studies to evaluate whether there is a beneficial physiological effect of an added non-digestible carbohydrate.

When the intervention study involves providing subjects with a whole food, along with an added non-digestible carbohydrate, the experimental and control diets should be similar enough that the relationship between the added non-digestible carbohydrate and beneficial physiological effect can be evaluated. The composition of the experimental and control diets should be similar for all food components, except for the added non-digestible carbohydrate of interest.

- *Were the relevant baseline data on the physiological endpoint (e.g., LDL cholesterol)) significantly different between the control and intervention group?*

Interpreting the findings of a dietary intervention study is difficult if the baseline values for the endpoint being measured are significantly different. For example, in a study on the effect of an added non-digestible carbohydrate on LDL cholesterol levels, having baseline LDL cholesterol levels higher in the intervention group than in the control group would lead to uncertainty as to whether any observed effect resulted from the difference in the intake of the added non-digestible carbohydrate between the two groups. Providing a "lead-in"[10] diet or a "wash-out" period[11] for studies with a cross-over design for an adequate duration prior to randomization can help reduce the likelihood of different baseline value biases.

- *How long was the study conducted?*

Studies that measure a physiological endpoint should be conducted long enough to ensure that any change in the endpoint results from the dietary intervention. If the study is run for a short time period so that the effects of the added non-digestible carbohydrate cannot be evaluated, then scientific conclusions cannot be drawn about the beneficial physiological effect of the non-digestible carbohydrate. Therefore, we would not consider such a study in our evaluation of the scientific evidence. For example, we consider 3 weeks to be the minimum duration for evaluating the effect of a dietary intervention on serum LDL cholesterol concentration (Kris-Etherton and Dietschy, 1997). Studies on bowel function are generally conducted for at least one week to account for a sufficient amount of time for collecting stool samples.

- *How were the results from the intervention and control groups statistically analyzed?*

Statistical analysis of the study data is critical because it provides the comparison between subjects consuming and not consuming the added non-digestible carbohydrate to determine whether there is a beneficial physiological effect. When conducting statistical analyses among more than two study groups, the data should be analyzed by a test

[10] A "lead-in" diet is one that is provided to all study groups prior to randomization.
[11] A "wash-out" period is the time period within a cross-over design study during which subjects do not receive an intervention.

designed for multiple comparisons (e.g., Bonferroni, Duncan). When statistical analyses are not performed between the control and intervention group or are conducted inappropriately, scientific conclusions cannot be drawn. Therefore, we do not intend to use such studies to evaluate whether there is a beneficial physiological effect of an added non-digestible carbohydrate.

- *Where were the studies conducted?*

It is important that the study population is relevant to the general U.S. population. Therefore, we intend to evaluate each study to determine, for example, if the study population lives in an area where malnutrition is common, and/or where the prevalence or etiology of the physiological effect that is being considered is not similar to that in the United States. Differences in nutrition, diet, and beneficial physiological effects between the United States and the country where a study was done may mean that the study results cannot be extrapolated to the U.S population. It may be difficult, for example, to draw scientific conclusions about the physiological effects of an added non-digestible carbohydrate in a population that consumes much higher or much lower levels of dietary fiber or other nutrients that have an effect on the physiological endpoint.

C. Evaluating the Strength of the Scientific Evidence

We will evaluate the strength of the evidence to determine whether there is a beneficial physiological effect of an added non-digestible carbohydrate using the scientific studies from which scientific conclusions can be drawn. We intend to conduct this evaluation by considering the number of studies and sample sizes of each study, the relevance of the body of scientific evidence to the U.S. population or target subgroup, whether study results supporting the beneficial physiological effect have been replicated,[12] and the overall consistency[13,14] of the total body of evidence. The findings for a beneficial physiological effect need to be replicated. Otherwise, the evidence will be insufficient. The consistency of findings indicates whether the evidence is sufficient to support a beneficial physiological effect.

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[12] Replication of scientific findings is important for evaluating the strength of scientific evidence (Wilson, 1990).

[13] In this guidance, "consistency" is used to mean the level of agreement among the studies from which scientific conclusions could be drawn about the non-digestible carbohydrate/beneficial physiological effect relationship**.**

[14] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill, 1965). See also Agency for Healthcare Research and Quality, Systems to Rate the Scientific Evidence, which defines “consistency” as “the extent to which similar findings are reported using similar and different study designs.” [http://www.ahrq.gov/clinic/epcsums/strengthsum.htm#Contents]

The studies are reviewed for:

- *Number* of studies and number of subjects per group.

- *Outcome* (beneficial effect, no effect, adverse effect) of the studies. For the outcome of an intervention study to demonstrate a beneficial physiological effect, the intervention group should be statistically significantly different from the control group ($P < 0.05$).

- *Consistency* of findings. In general, the greater the consistency among the studies in showing a beneficial physiological effect, the higher the level of confidence that a relationship between an added non-digestible carbohydrates and a beneficial physiological effect exists. Conflicting results do not disprove an association because the elements of the study design may account for the lack of an effect in negative studies, but conflicting results tend to weaken confidence in the strength of the association.

- *Relevance* to the general U.S. population. For example,

  To what extent did the studies that showed a benefit include populations that are relevant to the general U.S. population?

  Do the studies suggest that the intake level of the added non-digestible carbohydrate that provides a beneficial physiological effect significantly exceeds levels that are typically consumed in the United States or that are considered to be unsafe?

We will evaluate whether the scientific evidence supports a beneficial physiological effect for the general U.S. population. If the evidence only supports finding a beneficial physiological effect for a subgroup, for example, only in children 1 through 3 years of age, we will consider that information to determine whether the beneficial physiological effect is appropriate for the declaration of the added non-digestible carbohydrate as a dietary fiber on the Nutrition Facts label on foods represented or purported to be specifically for that subgroup.

IV. References

We have placed the following references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of November 17, 2016, FDA had verified the Web site address for the references it makes available as hyperlinks from the Internet copy of this guidance,

but FDA is not responsible for any subsequent changes to Non-FDA Web site references after November 17, 2016.

1. Dietary Guidelines for Americans, 2015-2020, 8th Edition. https://health.gov/dietaryguidelines/2015/guidelines/

2. 21 CFR 101.77. Health claims: fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, and risk of coronary heart disease. https://www.gpo.gov/fdsys/pkg/CFR-2003-title21-vol2/pdf/CFR-2003-title21-vol2-sec101-77.pdf

3. FDA. 2009. Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims. http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm073332.htm

4. Greer N, Mosser G, Logan G, Halaas GW. A practical approach to evidence grading. *Joint Commission Journal on Quality Improvements* 2000; 26:700-712.

5. Hill AB. The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine* 1965; 58:295-300.

6. Institute of Medicine. Dietary Supplements: A Framework for Evaluating Safety. The National Academies Press, Washington, DC. 2005.

7. Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids. The National Academies Press, Washington, DC. 2002.

8. Institute of Medicine. Dietary Reference Intakes. Proposed Definition of Dietary Fiber. The National Academies Press, Washington, DC. 2001.

9. Kraemer HC, Lowe KK, Kupfer DJ. To Your Health: How to Understand What Research Tell Us About Risk. Oxford University Press, 2005.

10. Federal Judicial Center, Reference Manual on Scientific Evidence, Third Edition, 2011.

11. Sempos CT, Liu K, Earnst ND. Food and nutrient exposures: what to consider when evaluating epidemiologic data. *American Journal of Clinical Nutrition* 1999; 69:1330S-1338S.

12. Spilker B. Guide to Clinical Studies. Raven Press, New York. 1991.

13. Topping D. Cereal complex carbohydrates and their contribution to human health. *Journal of Cereal Science* 2007; 46:220-229.

14. Wilson E.B. An Introduction to Scientific Research. Dover Publications, New York. 1990.