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Office of Disease Prevention and Health Promotion
U.S. Department of Health and Human Services

Admiral Rachel L. Levine, MD
Assistant Secretary for Health
U.S. Public Health Service
U.S. Department of Health and Human Services

Re: Scientific Questions to be Examined to Support the Development of the Dietary Guidelines for Americans 2025-2030; Docket No. HHS-OASH-2022-0005

Dear Ms. de Jesus and Ms. Levine,

Thank you for this opportunity to provide public comment on the scientific questions to be examined in order to develop the 2025-2030 *Dietary Guidelines for Americans* (DGA).

I am a Research Nutritional Biologist in the Department of Molecular Biosciences, University of California Davis, and a Registered Dietitian for more than 40 years. I have served as Acting PI or PI on five NIH/NHLBI-funded dietary intervention studies on the health effects of added sugar consumption and have authored/co-authored 19 reviews and book chapters on the topic. I do not undertake any industry-sponsored research, nor am I funded by any corporate interests.

My comment relates to proposed questions related to **Added Sugars.**

USDA/HHS Proposed questions**:**

What is the relationship between beverage consumption (beverage patterns, dairy milk and milk alternatives, 100% juice, low- or no-calorie sweetened beverages, sugar-sweetened beverages, coffee, tea, water) and:

- growth, size, body composition, risk of overweight and obesity, and weight loss and maintenance?
- risk of type 2 diabetes?

What is the relationship between food sources of added sugars consumed and:

- growth, size, body composition, risk of overweight and obesity, and weight loss and maintenance?
- risk of type 2 diabetes?

With this comment I should like to recommend a critical additional proposed question:

Does consumption of added sugar have detrimental effects on risk factors for cardiometabolic disease that are independent of changes in body weight?

Here, I offer a recent published study as well as data from a recently-completed NIH-funded study that provide evidence that it does.

The results from the first randomized controlled phase 2 clinical trial testing the administration of a fructokinase inhibitor in participants with Non-Alcoholic Fatty Liver Disease (NAFLD) were recently published.[1] The fructokinase inhibitor (PF-06835919) led to a 26.5% reduction in liver fat, an 11.5% reduction in fasting uric acid, and a trend for improvements of other cardiometabolic parameters, including insulin resistance and inflammation.[1] This study documents the mechanistic role of fructokinase in mediating the unregulated hepatic fructose uptake and overload that leads to metabolic dysregulation. It is also worth noting that the favorable effects of the fructokinase inhibitor were accompanied by a small (< 1 kg), but significant, increase of body weight.[1] This is in contrast to dietary intervention trials in which increases or decreases in fructose/sugar intake often induce parallel changes in risk factors and body weight, thus making it difficult to differentiate direct metabolic effects of sugar from those that are mediated by changes of body weight. However, in this study, preventing hepatic fructose overload via inhibition of fructokinase led to decreased liver lipid content and favorable metabolic effects that are clearly not confounded by favorable effects on body weight.
It is my considered opinion that this new evidence from Kazierad et al.[1] refutes the older contention of Kahn and Sievenpiper[2] that dietary sugars are purely a highly palatable source of energy that have no unique or detrimental impact relative to any other source of calories.

Further, the findings of Kazierad et al. are supported by new, as yet unpublished results from the work of the Havel/Stanhope research team. The following summarizes early results from 'Adverse metabolic effects of dietary sugar' (5 R01 HL121324, 8/2014-5/31/2021; PI: PJ Havel)**:**

> We compared the metabolic effects of consuming beverages sweetened with high fructose corn syrup (HFCS: 25% of calculated energy requirement) or with aspartame in healthy, normal weight men and women. During the 2-week baseline period and the 4-week intervention period, the 37 participants were restricted to consuming only the

[1] Kazierad DJC, Chidsey K, Somayaji VR, Bergman AJ, Birnbaum MJ, Calle RA. Inhibition of ketohexokinase in adults with NAFLD reduces liver fat and inflammatory markers: A randomized phase 2 trial Clinical Advances 2 (2021) 800-813.
[2] Kahn R, Sievenpiper JL. Dietary sugar and body weight: have we reached a crisis in the epidemic of obesity and diabetes?: We have, but the pox on sugar is overwrought and overworked. Diabetes Care 37 (2014) 957-62.

experimental diet and drinks. The experimental diets were formulated to ensure that the experimental groups (HFCS vs aspartame) consumed diets that were matched for macronutrient distribution and fiber. The early results demonstrate that HFCS-SB induced significant increases of de novo lipogenesis and circulating triglyceride and uric acid compared with aspartame-SB. **These significant differences occurred even though subjects consuming HFCS-SB exhibited modest, but significant weight loss over the 4-week intervention period that was comparable to the weight loss in subjects consuming aspartame-SB.** These results provide strong evidence to support our hypothesis that HFCS-SB negatively affects metabolic disease risk factors through mechanisms that are independent of body weight gain.

Additionally, based on my extensive expertise in performing dietary intervention studies on the health effects of added sugars, I should like to recommend that the Departments **consider whether GRADE be used to evaluate the quality of nutritional evidence.**

Here, I provide two contradictory viewpoints for your consideration:

In 2017, Erickson et al.[3] used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method to assess the evidence quality of research articles supporting guideline recommendations to lower added sugar consumption. The authors describe GRADE as a transparent framework for developing and presenting summaries of evidence and state it provides a systematic approach for making clinical practice recommendations. Using GRADE, they conclude that guidelines on dietary sugar do not meet criteria for trustworthy recommendations and are based on low-quality evidence and state that public health officials (when promulgating these recommendations) and their public audience (when considering dietary behavior) should be aware of these limitations.

However, more recently Jukola[4] evaluated the application of evidentiary standards originating from evidence-based medicine in nutrition advice. The analysis shows that it is problematic to criticize nutrition recommendations for not being based on randomized controlled trials. Due to practical, ethical and methodological and reasons, it is difficult to conduct rigorous randomized controlled trials for acquiring evidence that is relevant for achieving the goals of population-level nutrition recommendations. Given the non-epistemic goals of the dietary recommendations, criteria of acceptable evidence should be adapted to the goals of the practice and the practical, ethical, and methodological constraints of the situation.

I should be delighted to discuss these concerns with you in more detail.

Yours sincerely,

Kimber Stanhope, PhD, MS, RD
Research Nutritional Biologist

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[3] Erickson J, Sadeghirad B, Lytvyn L, Slavin J, Johnston BC. The Scientific Basis of Guideline Recommendations on Sugar Intake: A Systematic Review. Ann Intern Med. 2017 Feb 21;166(4):257-267.
[4] Jukola S**.** On the evidentiary standards for nutrition advice. Stud Hist Philos Biol Biomed Sci. 2019 Feb;73:1-9.

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