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Department of Health and Human Services
Food and Drug Administration
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Submitted March 19, 2024, via http://www.regulations.gov at Docket No. FDA 2013-S-0610 pursuant to 21 C.F.R. § 10.30

CITIZEN PETITION

The undersigned submits this petition under the citizen petition regulations of the Federal Food, Drug, and Cosmetic Act to request that the Commissioner of Food and Drugs withdraw a March 2024 letter of enforcement discretion, and cease exercising enforcement discretion, for qualified health claims about yogurt and reduced risk of type 2 diabetes.

A. ACTION REQUESTED

The Physicians Committee for Responsible Medicine requests that the Commissioner:

(1) withdraw in its entirety the letter of enforcement discretion dated March 1, 2024, regarding qualified health claims about yogurt and reduced risk of type 2 diabetes; and
(2) cease exercising enforcement discretion for qualified health claims about yogurt and reduced risk of type 2 diabetes.

B. STATEMENT OF GROUNDS

In December 2018, Danone North America ("Danone") submitted a qualified health claim petition to the Food and Drug Administration ("FDA"), Docket No. FDA-2019-P-1594, seeking to include the following claims on its yogurt labels:

- "Eating yogurt regularly may reduce the risk of type 2 diabetes. FDA has concluded there is limited information supporting this claim."
- "Eating yogurt regularly may reduce the risk of type 2 diabetes according to limited scientific evidence."

On March 1, 2024, FDA responded to Danone's petition by announcing that it intends to consider exercising enforcement discretion for these qualified health claims:

- "Eating yogurt regularly, at least 2 cups (3 servings) per week, may reduce the risk of type 2 diabetes. FDA has concluded that there is limited information supporting this claim."
- "Eating yogurt regularly, at least 2 cups (3 servings) per week, may reduce the risk of type 2 diabetes according to limited scientific evidence."

FDA, *Enforcement Discretion Letter for Yogurt and Type 2 Diabetes dated March 1, 2024*, https://www.regulations.gov/document/FDA-2019-P-1594-0146.

FDA stated that if "new information is submitted to the agency, FDA intends to evaluate the new information that becomes available to determine whether it necessitates a change in this decision." *Id.* FDA recognized that "scientific evidence may become available that will support significant scientific agreement, that will no longer support the use of the above qualified health claims, or that may raise safety concerns about the substances that are the subject of the claims." *Id.*

This citizen petition submits new information, set forth below, that warrants a change in FDA's decision to exercise enforcement discretion with respect to the qualified health claims. An insufficiently supported qualified health claim for a food product can mislead consumers and put them at risk insofar as they might use an unsupported dietary step instead of effective means of protecting their health. Moreover, the qualified health claim could be easily misinterpreted to suggest that dairy products in general or probiotic products may reduce diabetes risk. Such misinterpretations can harm consumers.

FDA Rejected Most of Danone's Supporting Evidence

Danone's petition cited 117 publications, including 50 observational studies, 33 interventional trials, 11 reviews, 8 meta-analyses, 9 publications relating to dietary intake and assessment tools, 3 reports, 2 position statements, and 1 methodological study. FDA assessed the reviews and meta-analyses as not providing sufficient information on the study population or nutrient composition of the yogurts included. These reviews and meta-analyses also did not provide sufficient information to allow FDA to critically review the study design and data analysis of the individual studies included to be able to draw scientific conclusions from them.

FDA assessed the interventional trials as not being sufficiently controlled to draw definitive scientific conclusions. The observational studies (including cohort and case-control studies) largely had methodological errors (such an insufficiently controlling for confounders or not excluding participants with type 2 diabetes at baseline), and for this reason FDA could not draw scientific conclusions from them.

Of the 117 studies submitted by Danone, FDA deemed sufficiently detailed for evaluation only the following handful of cohort studies, each of which found only modest associations between yogurt intake and diabetes risk:

The **Women's Health Study** followed 37,183 women for an average of 10 years follow up.[1]

> **Results:** Consuming yogurt ≥ 2x per week compared to < 1x per month was associated with reduced risk of type 2 diabetes incidence (RR 0.82, p=0.03).
>
> **Confounders adjusted for:** Total energy intake, randomized-treatment assignment, age, family history of diabetes (yes/no), smoking status (never smoked, former smoker, or current smoker), BMI (continuous), hypercholesterolemia (yes/no), hypertension (yes/no), hormones

(past, current, or never), physical activity (quintiles of METs), alcohol consumption (rarely/never, 1–3 drinks/month, 1–6 drinks/week, or >1 drink/day), dietary intakes (quintiles) of fibers, total fat, dietary glycemic load, dietary calcium, vitamin D, and magnesium.

The **Nurses' Health Study ("NHS") I** followed 121,700 women for up to 30 years.[2]

Results: Consuming yogurt >2 per week compared to <1 per month was associated with slightly reduced risk of type 2 diabetes incidence (RR 0.84, p=<0.001).

Confounders adjusted for: Age (continuous), BMI (eight categories), total energy intake (quintiles), race, smoking, physical activity, alcohol consumption, menopausal status and menopausal hormone use (NHS I and II participants only), oral contraceptive use (NHS II participants only), diabetes family history, hypertension, hypercholesterolemia, trans-fat intake, glycemic load, red and processed meat intake, nuts intake, sugar-sweetened beverage intake, coffee intake, and other dairy types for individual dairy types.

The **Women's Health Initiative Observational Study** followed 82,076 postmenopausal women for a mean 7.9 years.[3]

Results: Women who were consuming yogurt >2x per week compared to <1x per week had a reduced risk for incident type 2 diabetes (RR 0.46, p=0.004).

Confounders adjusted for: Age, race/ethnicity, total energy intake, income, education, smoking, alcohol intake, family history of diabetes, use of postmenopausal hormone therapy, systolic blood pressure, diastolic blood pressure, BMI, physical activity, an interaction term between quintiles of yogurt intake and time, dietary glycemic load, total fat, fiber, and total magnesium.

The **PREDIMED study** followed 3,454 people for a median of 4.1 years.[4]

Results: Compared with tertile 1 of yogurt intake, individuals in tertile 3 had a reduced risk of type 2 diabetes as follows: Total yogurt (HR 0.60, p=0.002), low-fat yogurt (HR 0.68, p=0.47), and whole-fat yogurt (HR 0.60, p=0.02).

Confounders adjusted for: Age, sex, BMI, dietary intervention group (MedDiet supplemented with virgin olive oil, and/or nuts, or control group), leisure time physical activity (MET-min/day), educational level (primary education, secondary education, or academic/graduate), smoking (never, former, or current smoker), hypertension, or antihypertensive use (yes/no), fasting glucose, HDL-cholesterol, triglyceride concentrations, cumulative average consumption of dietary variables in energy-adjusted quintiles (vegetables,h legumes, fruits, cereals, meat, fish, olive oil, and nuts) alcohol and alcohol squared in g/day.

Another **PREDIMED study** analysis followed 3,349 people for 4.3 years.[5]

> **Results:** 125g whole-fat yogurt was associated with a lower risk of incident diabetes of (HR 0.65, p=0.02). The highest quartile of saturated and animal fat intakes had a higher risk of diabetes than the lowest quartile: (HR 2.19, p-trend = 0.01) and (HR 2.00, p-trend=<0.01) respectively.
>
> **Confounders adjusted for:** Age, sex, intervention group, BMI (in kg/m2), smoking status, educational status, leisure-time physical activity, baseline hypertension or the use of antihypertensive medication, hypercholesterolemia or the use of lipid-lowering drugs, fasting plasma glucose, yearly updated total energy intake, alcohol intake, and the intake of vegetables, fruits, legumes, cereals, fish, meat, dairy, olive oil, nuts, and biscuits (except if the exposure was included in these food groups).

Another **PREDIMED study** analysis followed 1,868 men and women for a median of 3.2 years.[6]

> **Results:** A higher yogurt intake was associated with reduced risk of metabolic syndrome (HR 0.72, p=0.001), while whole-fat dairy consumption was not significantly associated with risk of metabolic syndrome.
>
> **Confounders adjusted for:** Intervention group; sex; age (year); leisure time physical activity (metabolic equivalent task day); BMI (kilograms per meter squared); current smoker (yes/no); former smoker (yes/no); use of hypoglycemic, hypolipidemic, antihypertensive, and insulin treatment at baseline; mean consumption during the follow-up of vegetables, fruit, legumes, cereals, fish, red meat, cookies, olive oil, and nuts (all grams per day), alcohol (grams per day and quadratic term); prevalence of MetS components at baseline, including abdominal obesity (yes/no), hypertriglyceridemia (yes/no), low HDL cholesterol (yes/no), hypertension (yes/no), and high fasting plasma glucose (yes/no).

In contrast to these findings, the Health Professionals Follow Up Study and the Nurses' Health Study II found no statistically significant relationship between yogurt and type 2 diabetes risk.[2]

The Health Professionals Follow Up Study followed 51,529 males for up to 24 years.[2]

> **Results:** Quintile 5 (3.59 servings per day) compared to quintile 1 (0.64 servings per day) was associated with a non-significant HR 0.99 (p=0.38).
>
> **Confounders adjusted for:** age (continuous), BMI (eight categories), total energy intake (quintiles), race, smoking, physical activity, alcohol consumption, diabetes family history, hypertension, hypercholesterolemia, trans-fat intake, glycemic load, red and processed meat intake, nuts intake, SSB intake, and coffee intake.

The Nurses' Health Study II followed 116,671 females for up to 16 years.[2]

> **Results:** Quintile 5 (3.85 servings per day) compared to quintile 1 (0.79 servings per day) was associated with a significantly lower risk when adjusted only for age, BMI, and daily energy, with an HR 0.90 (p=<0.001). However, when additionally adjusted for dietary and other non-dietary factors, this association was no longer statistically significant, with an HR 1.02 (p=0.99).
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> **Confounders adjusted for:** age (continuous), BMI (eight categories), total energy intake (quintiles), race, smoking, physical activity, alcohol consumption, menopausal status and menopausal hormone use, oral contraceptive use, diabetes family history, hypertension, hypercholesterolemia, trans-fat intake, glycemic load, red and processed meat intake, nuts intake, SSB intake, and coffee intake.

Substantial Limitations Render FDA's Evaluation Insufficient

1. Observational studies have yielded inconsistent results. The vast majority, including some of the best-controlled studies, do not support the health claim.

The data presented in support of the claim that yogurt reduces the risk of type 2 diabetes are observational, and findings are inconsistent. FDA rejected most of the references in Danone's petition due to the limitations mentioned above. Of the observational data, most cohorts cited, including the Health Professionals Follow Up Study and the Nurses' Health Study II, found no statistically significant relationship between yogurt and type 2 diabetes risk.[2]

Observational epidemiology cannot establish a causal relationship based on a few cohort studies alone. The Bradford Hill criteria are commonly used to attempt to identify a causal relationship, and these criteria include the following components:[7]

1.1 Strength of association: The strength of the risk reduction varies between studies but is often small.
1.2 Consistency: As noted by FDA, there is a lack of consistently reduced risk of type 2 diabetes in response to yogurt consumption in the cohort studies cited.
1.3 Specificity: The Bradford Hill criteria suggest that a relationship is more likely to be causal when one exposure leads to the outcome of one disease. In the case of type 2 diabetes, evidence suggests that the overall dietary pattern appears to be more important than a single specific food.[8–11]
1.4 Temporality: The cohort studies show temporality in that the exposure to yogurt preceded the type 2 diabetes; however, without additional randomized controlled trials, reverse causation cannot be ruled out.
1.5 Biological gradient: There is no clear dose-response relationship between the amount of yogurt consumed and the risk of type 2 diabetes.
1.6 Plausibility: A plausible biological mechanism by which yogurt is protective against type 2 diabetes has not been identified.
1.7 Coherence: In the case of yogurt and diabetes risk, there is no coherence among observational research, interventional trials, and biological plausibility/mechanistic data.

1.8 Experiment: The Bradford Hill criteria note that animal studies may play a role in attempting to show causation. While this is a highly controversial area, we note that such data do not exist.
1.9 Analogy: Analogy means when one causal agent is known, a second causal agent that is similar in some way can be accepted with weaker evidence in support. There is no analogous support in the case of yogurt, as research has not established a causal protective effect of the intake of total or other dairy products.

2. There are no randomized controlled trials or mechanistic data in support of the claim.

Randomized controlled trials allow for control of exposures and confounders. There are no adequate randomized controlled trials in Danone's petition to support a claim that yogurt might be protective, nor are there are mechanistic data to show how yogurt might be protective. This type of data is important in establishing a causal relationship.

3. The evidence failed to adjust for confounding based on socio-economic status.

People who consume more yogurt may tend to be in higher socioeconomic groups, compared to nonconsumers and are therefore at a lower risk of type 2 diabetes regardless of yogurt intake. Data from the U.S. National Health and Nutrition Examination Survey found a statistically significant relationship between socioeconomic status and risk of type 2 diabetes and that this effect might be mediated by alcohol and physical activity, which were adjusted for in the cohort studies mentioned above, as well as health care, for which there was no adjustment.[13]

4. Dietary pattern is more important for health effects than an individual food is.

Vegan and vegetarian dietary patterns have been associated with a lower risk of type 2 diabetes, as seen in American, British, and Asian populations.[8–11] The healthful plant-based diet index ("hPDI"), which has its limitations, positively scores plant-based whole foods such as fruits, vegetables, and whole grains, and negatively scores animal-based foods including dairy products. A higher hPDI score has consistently been associated with a lower risk of type 2 diabetes.[13–16]

The Qualified Health Claims are Not Supported by Evidence

Research studies do not sufficiently support a protective effect of yogurt on type 2 diabetes risk, nor are they sufficient for recommending the consumption of any individual food product. Allowing a qualified health claim with little supporting evidence harms consumers by encouraging them to take the unproven step of adding to their diets a source of calories, rather than making effective lifestyle changes known to reduce diabetes risk, such as weight loss, a plant-based diet, or exercise. The presence of a qualified health claim on a food product might lead consumers to ignore recommendations to include in their diets other health-promoting foods that lack a qualified health claim on their packaging.

In the context of a qualified health claim, consumers might speculate as to the mechanism for the supposed health effect, assuming that something in dairy products or in probiotics is responsible for a presumed benefit. Consumers might then turn to other dairy products or probiotic

supplements, and these are unlikely to be beneficial. Consumers might inadvertently assume that all yogurt, dairy, or probiotic products offer similar health effects, leading to an increased consumption of products that offer no health benefit.

A qualified health claim regarding yogurt and reduced risk of type 2 diabetes has the potential to mislead consumers and to put them at risk. Therefore, FDA must withdraw its letter of enforcement discretion, and cease exercising enforcement discretion, for such any such claims.

C. ENVIRONMENTAL IMPACT

The requested action is excluded under the provisions of 21 C.F.R. § 25.30(k).

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b)(3), this information will be submitted if requested by the Commissioner following review of the petition.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully Submitted,

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