Children's Hospital of Philadelphia

DIVISION OF GASTROENTEROLOGY, HEPATOLOGY & NUTRITION

3401 Civic Center Blvd, Philadelphia, PA 19104, www.chop.edu/gastroenterology

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Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments on "Evaluating the Public Health Importance of Food Allergens Other Than the Major Food Allergens Listed in the Federal Food, Drug, and Cosmetic Act: Guidance for FDA Staff and Stakeholders – Draft Guidance", FDA Docket Number: FDA-2021-N-0553 ("FDA's Draft Guidance")

Dear Dr. Mayne and Deputy Commissioner Yiannas:

As an attending physician in the Division of Gastroenterology, Hepatology, and Nutrition and Co-Director of the Center for Celiac Disease at the Children's Hospital of Philadelphia, I am writing to provide my comments on FDA Docket Number: FDA-2021-N-0553.

The Center for Celiac Disease has treated more children with celiac disease than any other institution in the nation. This includes more than 3,200 patients and their families with celiac disease, wheat allergy and gluten-sensitivity in the past five years. Unfortunately, there is an unbelievable number of children affected by gluten – and those numbers continue to rise.

In addition to gastrointestinal and extraintestinal symptoms, one of greatest challenges impeding the wellbeing for patients with celiac disease is the fear of "being glutened" and the long-term damage it may cause. Research at CHOP has found that increased stress and the daily struggle with ensuring safe food – compounded by the issues of food labeling – can have devastating effects on quality of life and potential rise in eating disorders, anxiety, and mental health illness.

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I agree with the National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Food and Nutrition Board; Committee on Food Allergies ("Food Allergy Committee"). "Finding a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management and Public Policy." The National Academies Press, 2016 (which was cited as FDA Ref. 2 in the FDA's Draft Guidance).[1]

The Food Allergy Committee's work for the National Academy of Sciences found that "Food allergy has two key classifications: immunoglobulin E (IgE)-mediated or non-IgE-mediated" (page 4) such as Celiac Disease. However, it should be noted that while there were certain references to Celiac Disease in the Food Allergy Committee's report, Celiac Disease was not covered in our report because it was "beyond the scope of the statement of task" for the Committee, not because Celiac is not an essential food allergen safety issue for the population.[2] I agree with the FDA that people with Celiac Disease "face potentially life-threatening illnesses if they eat gluten, typically found in breads, cakes, cereals, pastas, and many other foods… There is no cure for celiac disease and the only way to manage the disease is to avoid eating gluten."[3]

According to the NIH's "Notice of Special Interest (NOSI): Accelerating Progress in Celiac Disease Research" that was published on November 23, 2021, there are more than 3 million Americans who have Celiac Disease.

> "Celiac disease is an autoimmune disease that occurs in genetically susceptible

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[1] https://www.ncbi.nlm.nih.gov/books/NBK435943/pdf/Bookshelf_NBK435943.pdf

[2] Following are discussion points about Celiac Disease in Ref. 2:

> "Other food-related diseases, such as celiac disease, or food intolerances, such as lactose intolerance, or toxicity of food additives, are not covered in this report because they were beyond the scope of the statement of task." (page 26) (emphasis added)
>
> "Non-IgE-mediated food allergy reactions (e.g., food protein induced enterocolitis) are less common and the mechanisms of the reactions are less well characterized. Celiac disease is a well-characterized, immune-mediated disease that has food as an exacerbating factor but will not be detailed in this report." (page 41) (emphasis added)
>
> "BOX C-2 Study Exclusion Criteria - Studies seeking to prevent potential manifestations of food allergy (e.g., atopic eczema/dermatitis or asthma) but not including an explicit diagnosis of sensitization to food or food allergy or studies investigating celiac disease were excluded, as well as management guidance documents, narrative reviews, letters to the editor, commentaries, studies that used animal or in vitro models, ecological studies, and studies of transplant patients." (page 448) (emphasis added)

[3] https://www.fda.gov/consumers/consumer-updates/gluten-free-means-what-it-says

individuals who develop an immune response to ingested gluten. This disease affects greater than 1% of the US population, and incidence appears to have been increasing over the last several decades. The only known treatment is life-long strict avoidance of all forms of wheat, rye, and barley. Although a gluten-free diet is an effective treatment in many individuals, recent research has revealed that up to 50% of individuals following a gluten-free diet are inadvertently exposed to gluten, and a substantial minority develop persistent or recurrent symptoms.

Clinical manifestations are multifaceted and include gastrointestinal (ranging from severe malabsorption to subclinical damage of the gastrointestinal tract) as well as extraintestinal (e.g., skin) expressions of disease. Additional manifestations may vary from subclinical damage of the gastrointestinal tract to refractory celiac disease that is non-responsive to a gluten-free diet. Although rare, celiac disease is associated with increased risk of gastrointestinal tract cancers and lymphomas."[4]

While a Non-IgE-Mediated food allergy is not capable of triggering anaphylaxis and being *immediately* life-threatening, Celiac disease patients face potentially life-threatening and severe adverse health effects that can arise through Gluten ingestion including by way of example and not limitation: anemia, cancer, heart disease, immunological scarring, intestinal damage, malnutrition, etc. [5] [6]

Nonetheless, the FDA's Draft Guidance appears to be inconsistent with the conclusions of international food safety authorities and expert committees comprised of scientists, regulators, physicians, clinicians and risk managers from academia, government and the food industry including:

- Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives. Evaluation of certain food additives and contaminants: fifty-third report of the Joint FAO/WHO Expert Committee on Food Additives. 2000. WHO Technical Report Series 896. World Health Organization, Geneva ("1999 FAO/WHO Expert

[4] https://grants.nih.gov/grants/guide/notice-files/NOT-AI-22-004.html
[5] https://www.fda.gov/media/157637/download
[6] https://www.congress.gov/event/117th-congress/senate-event/LC65823/text?s=1&r=42 ; "Patient Perception of Treatment Burden is High in Celiac Disease Compared to Other Common Conditions," PMC, National Library of Medicine, National Institutes of Health, July 1, 2014, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159418/ ; Roy, A., Minaya, M., Monegro, M. et al. Partner Burden: A Common Entity in Celiac Disease. Dig Dis Sci 61, 34513459 (2016), https://doi.org/10.1007/s10620-016-4175-5; and "What is Celiac Disease?", Celiac Disease Foundation, https://celiac.org/about-celiac-disease/what-is-celiac-disease/

Consultation"; also referred to as the "1999 Codex criteria" as detailed in the FDA's Draft Guidance and cited as "FDA Ref. 25").[7]

- Food and Agriculture Organization of the United Nations/World Health Organization. "Summary report of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens. Part 1: Review and validation of Codex priority allergen list through risk assessment." 2021 ("2021 FAO/WHO Expert Consultation"; also referred to as "FDA Ref. 45" in FDA's Draft Guidance).[8]

For example, the 1999 FAO/WHO Expert Consultation determined:

> "The revised list of those foods and ingredients known to cause food allergies and intolerance and whose presence should always be declared was identified as the following: cereals containing gluten (i.e. wheat, rye, barley, oats, spelt or their hybridized strains) and their products; Crustacea and products of these; Egg and egg products; Fish and fish products; Peanuts, soybeans, and products of these; Milk and milk products (lactose included); Tree nuts and nut products; and Sulfites in concentrations of 10 mg/kg or more."[9]

As our Food Allergy Committee found,

> "The 1999 CAC [Codex Alimentarius Commission] priority list included milk, egg, fish, crustacean shellfish, peanut, soybean, tree nuts, cereal grain sources of gluten, and sulfites. Several of these items were added because the FAO [Food and Agriculture Organization of the United Nations] Technical Consultation also considered celiac disease, intolerances, and sensitivity reactions in addition to immunoglobulin E (IgE)-mediated food allergies in its deliberations. For example, gluten was included because of its association with celiac disease." (page 284)
>
> "In the United States, the priority list of allergenic foods was established by the Congress with the passage of the Food Allergen Labeling and Consumer Protection Act,6 7 ['For an analysis on Food Allergen Labeling and Consumer Protection Act see Derr (When Food Is Poison), 2006.'] (FALCPA) of 2004. The FALCPA list mirrored the 1999 CAC list except that the FALCPA list did not address celiac disease and therefore did not recognize cereal sources of gluten as major allergenic foods." (page 286)

The 2021 FAO/WHO Expert Consultation, which was chaired by the FDA's Dr. Lauren Jackson, Chief, Process Engineering Branch, Division of Processing Science & Technology, Institute for Food Safety & Health, determined:

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[7] https://apps.who.int/iris/bitstream/handle/10665/42378/WHO_TRS_896.pdf
[8] http://www.fao.org/3/cb4653en/cb4653en.pdf
[9] https://apps.who.int/iris/bitstream/handle/10665/42378/WHO_TRS_896.pdf

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> "Based on systematic and thorough assessments which used all three criteria (prevalence, severity and potency), the Committee recommended that the following should be listed as priority allergens: Cereals containing gluten (i.e., wheat and other Triticum species, rye and other Secale species, barley and other Hordeum species and their hybridized strains), crustacea, eggs, fish, milk, peanuts, sesame, specific tree nuts (almond, cashew, hazelnut, pecan, pistachio and walnut)."[10] [11]

While FDA Ref. 25 and FDA Ref. 45 are cited as sources in the FDA's Draft Guidance, the FDA's Draft Guidance does not include key findings by the "scientists, regulators, physicians, clinicians, and risk managers from academia, government and the food industry", and their conclusions to always declare (label) Gluten on food product labels in order to provide consumer protection for the Celiac community to whom ingesting Gluten is just like eating poison and potentially life-threatening.

The global implementation of FDA Ref. 25 and FDA Ref. 45 can be seen in how more than 85 countries worldwide require that Gluten be labeled on all packaged foods, according to the map and chart produced by the Food Allergy Research and Resource Program at the University of Nebraska-Lincoln.[12]

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[10] "Due to the lack of data on prevalence, severity and/or potency, or due to regional consumption of some foods, the Committee recommended that some of the allergens, ... oats, ... should not be listed as global priority allergens but may be considered for inclusion on priority allergen lists in individual countries."

[11] http://www.fao.org/3/cb4653en/cb4653en.pdf

[12] https://farrp.unl.edu/IRChart

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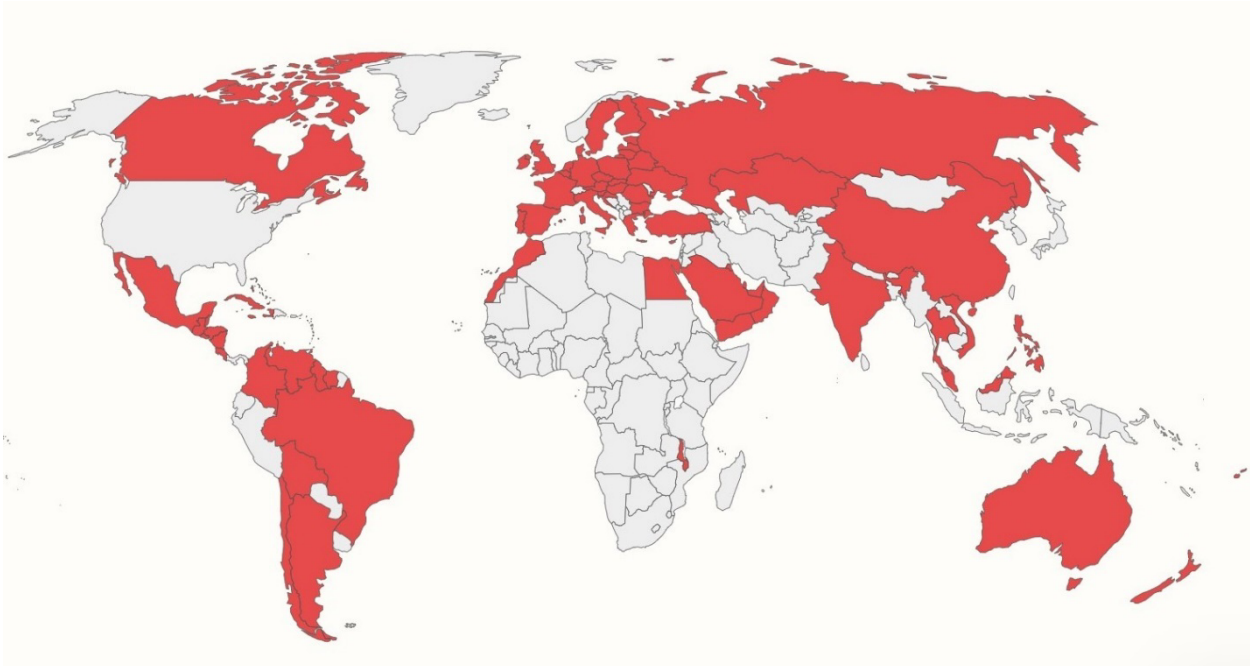

The Venn diagram below illustrates the key near-peer similarities between food allergies that are Non-IgE-Mediated Mechanisms with Celiac Disease (Gluten) and typical IgE-Mediated Mechanisms: potentially life-threatening, the only treatment is to strictly avoid the food allergen(s), and consumers' reliance on food labels to know what is safe to eat.

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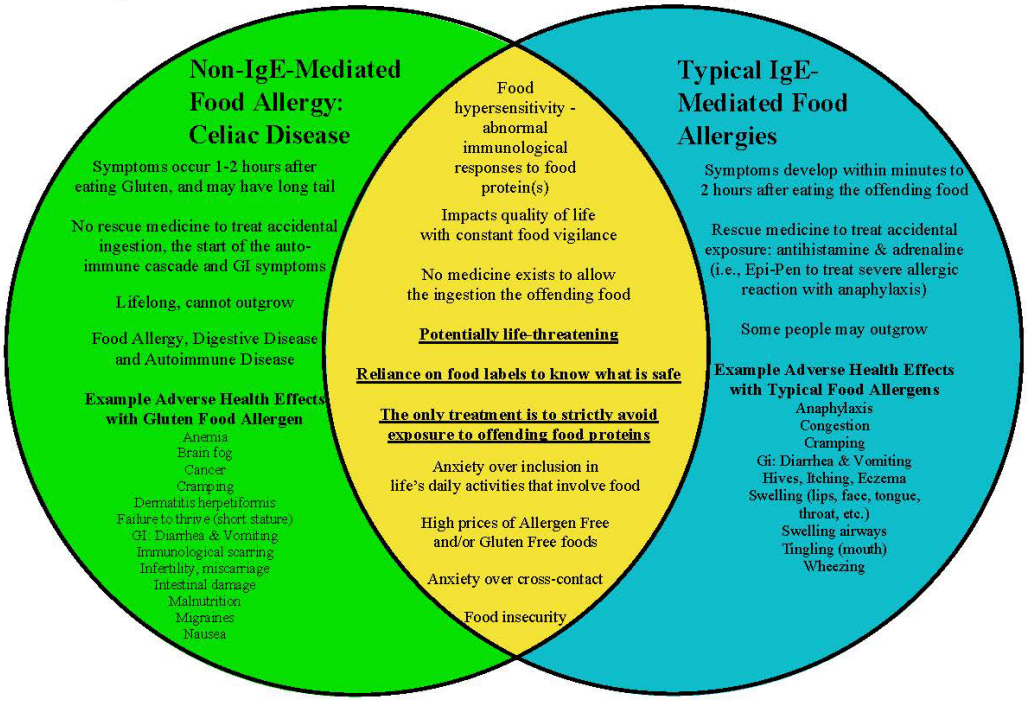
What is Food Allergy?
The Similarities and Differences Between
Non-IgE-Mediated Mechanisms with Celiac Disease & Typical IgE-Mediated Mechanisms



Importantly, unlike food allergies with IgE-Mediated mechanisms, there is no rescue medicine (i.e., adrenaline or antihistamine) to treat accidental ingestion of Gluten and the start of the auto-immune cascade in food allergy with Non-IgE-Mediated mechanisms such as Celiac Disease. Additionally, those with a Non-IgE-Mediated food allergy to Gluten cannot outgrow their food allergy – Celiac is lifelong (until such time as a cure may be developed).[13]

While U.S. consumers' reactions to a top 8 major food allergens (plus sesame as of January 1, 2023) and Gluten vary, their consumer habits are the same -- they avoid purchasing foods that contain the allergen(s) that cause a potentially life-threatening immunological adverse reaction.

However, the key difference from a consumer protection standpoint is that under the Food Allergen Labeling and Consumer Protection Act of 2004 ("FALCPA"), the labeling scheme for

[13] This diagram graphic is intended to convey that Non-IgE-Mediated food allergy with Celiac Disease and typical IgE-Mediated food allergies are both really dangerous and deserve equal treatment with respect to consumer protection with food labeling. The adverse health effects are listed in alphabetical order, and these health dangers are an illustrative, but not exhaustive list. This diagram expands and updates information as was included in Table 2-1 in "Finding a Path to Safety in Food Allergy", FDA Ref. 2 in FDA's Draft Guidance.

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the top 8 major food allergens in the U.S. is mandatory, but the labeling of Gluten is permissive. Wheat is required to be labeled, but Gluten is not. Gluten is found in Wheat, Barley, Rye and most Oats. Just because something is Wheat free does not mean its Gluten Free. In other words, whereas sufferers of the current top 9 Major Food Allergens in the U.S. rely on what ingredients are expressly included in required labeling disclosures of packaged foods, the Celiac community must rely only on what ingredients are excluded in voluntary Gluten Free labeling disclosures on packaged foods.

I believe that a Gluten Free diet is not all that is needed to treat Celiac Disease; rather a Gluten Free diet is all that has ever been historically available to treat Celiac Disease. Additionally, with respect to labeling food products in the United States, the voluntary Gluten Free labeling scheme does not sufficiently protect consumers who are on medically required and very restrictive Gluten Free diets.

I want to share my strong recommendation that Gluten be labeled on all packaged foods in the United States, in accordance with the 2021 FAO/WHO Expert Consultation, just like it is in more than 85 countries around the world. I am respectfully requesting that the FDA draft guidance be revised to include evaluating Gluten as a food allergen and changing the voluntary labeling rule to a mandatory labeling rule to keep 3 million Americans with Celiac Disease safe.

Sincerely,

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