



DIVISION OF GASTROENTEROLOGY,
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Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
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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the Major Food Allergens Listed in the Federal Food, Drug, and Cosmetic Act: Guidance for FDA Staff and Stakeholders – Draft Guidance”, FDA Docket Number: FDA-2021-N-0553 (“FDA’s Draft Guidance”)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 a pediatric gastroenterologist in the Division of Gastroenterology, Hepatology and Nutrition at Children’s Hospital of Philadelphia, I am writing to provide my comments on FDA Docket Number: FDA-2021-N-0553. I am a physician-scientist with a laboratory studying mechanisms of inflammation in non-IgE mediated food allergy (specifically eosinophilic gastrointestinal disorders) and I have a clinical practice dedicated to taking care of children with these disorders.

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 and Eosinophilic Esophagitis (EoE). However, it should be noted that while there were certain references to Celiac Disease and non-IgE mediated food allergies in the Food Allergy Committee’s report, these were not covered in our report because they were “beyond the scope of the statement of task” for the Committee, not because Celiac/EoE are not an essential food safety issue for the population.¹

¹ Following are discussion points about Celiac Disease in FDA Ref. 2 as cited in the FDA’s Draft Guidance:

Eosinophilic esophagitis, or EoE, is a chronic allergic disease that affects pediatric patients and adults alike. In the setting of exposure to foods that are ubiquitous in the American diet, most commonly milk and gluten, an inflammatory process occurs in the esophagus leading to esophageal damage and narrowing.

Celiac Disease is an autoimmune disorder in which exposure to gluten containing foods, causes, “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.”²

Taken together, these two entities, Celiac Disease and EoE represent non-IgE mediated food allergies that would greatly benefit from specific gluten labeling.

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 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

“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)

² <https://www.fda.gov/consumers/consumer-updates/gluten-free-means-what-it-says>

non-responsive to a gluten-free diet. Although rare, celiac disease is associated with increased risk of gastrointestinal tract cancers and lymphomas.”³

Recent epidemiologic studies on EoE demonstrate that it affects approximately 57/100,000 individuals (Dellon and Hirano *Gastroenterology*). The incidence and prevalence of EoE is rising in the United States and world-wide. In the pediatric population, exposure to offending food particles causes patients to experience feeding difficulties, failure to thrive, growth arrest, and profuse vomiting. Adolescents and adults experience food becoming stuck in the esophagus requiring emergent endoscopy to dislodge and are at risk for esophageal perforation which is a potentially deadly complication of EoE.

While a Non-IgE-Mediated food allergy is not capable of triggering anaphylaxis and being *immediately* life-threatening, Celiac Disease and EoE 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 for Celiac Disease and esophageal stricture, recurrent food impaction and esophageal perforation for EoE.^{4 5}

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 Consultation”; also referred to as the “1999 Codex criteria” as detailed in the FDA’s Draft Guidance and cited as “FDA Ref. 25”).⁶
- 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).⁷

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

³ <https://grants.nih.gov/grants/guide/notice-files/NOT-AI-22-004.html>

⁴ <https://www.fda.gov/media/157637/download>

⁵ <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/>

⁶ https://apps.who.int/iris/bitstream/handle/10665/42378/WHO_TRS_896.pdf

⁷ <http://www.fao.org/3/cb4653en/cb4653en.pdf>

“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.”⁸

The 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:

“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).”^{9 10}

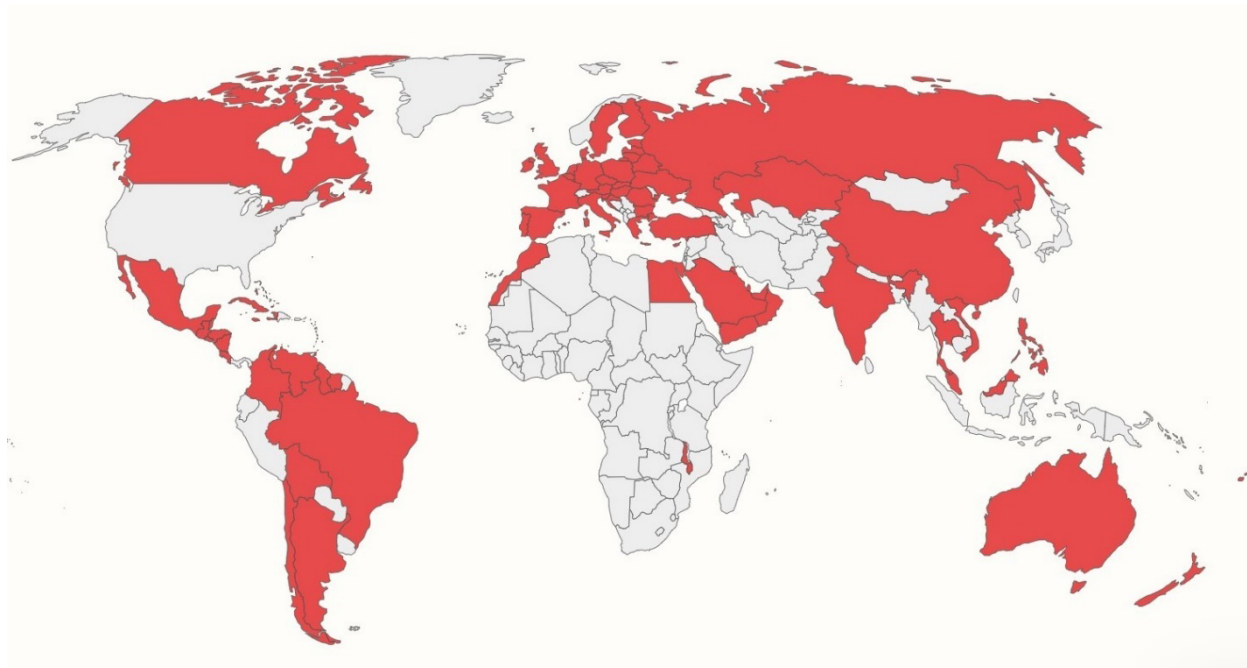
While FDA Ref. 25 and FDA Ref. 45 are cited as sources in the FDA’s Draft Guidance, the FDA’s Draft Guidance does not include key findings by the “scientists, regulators, physicians, clinicians, and risk managers from academia, government and the food industry”, and their conclusions to always declare (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.

⁸ https://apps.who.int/iris/bitstream/handle/10665/42378/WHO_TRS_896.pdf

⁹ “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.”

¹⁰ <http://www.fao.org/3/cb4653en/cb4653en.pdf>

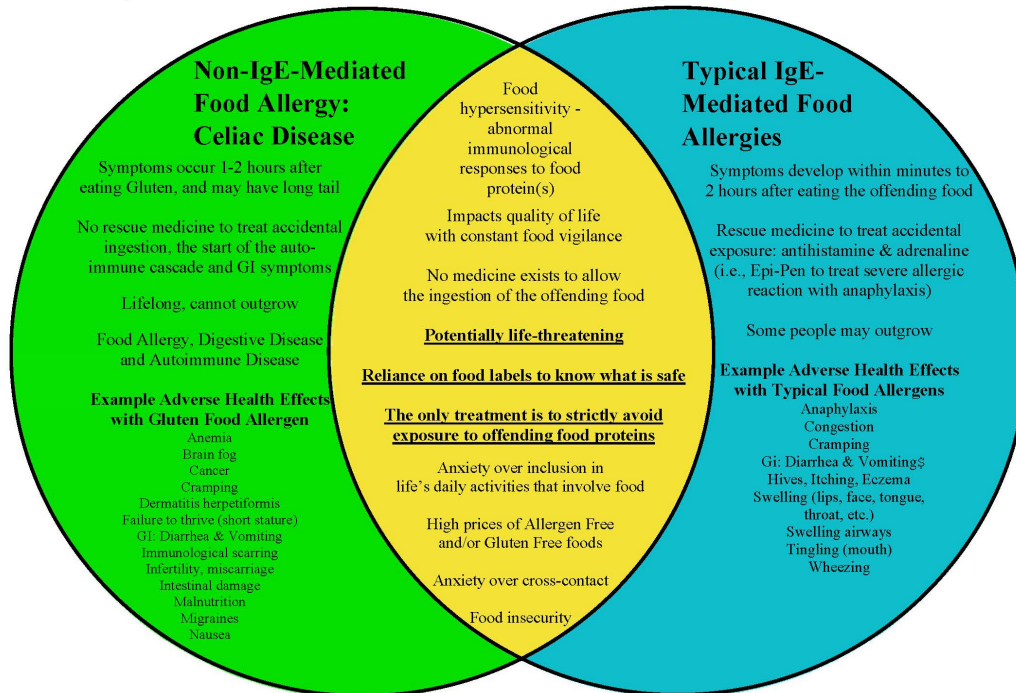
The global implementation of FDA Ref. 25 and FDA Ref. 45 can be seen in how more than 85 countries worldwide require that Gluten be labeled on all packaged foods, according to the map and chart produced by the Food Allergy Research and Resource Program at the University of Nebraska-Lincoln.¹¹



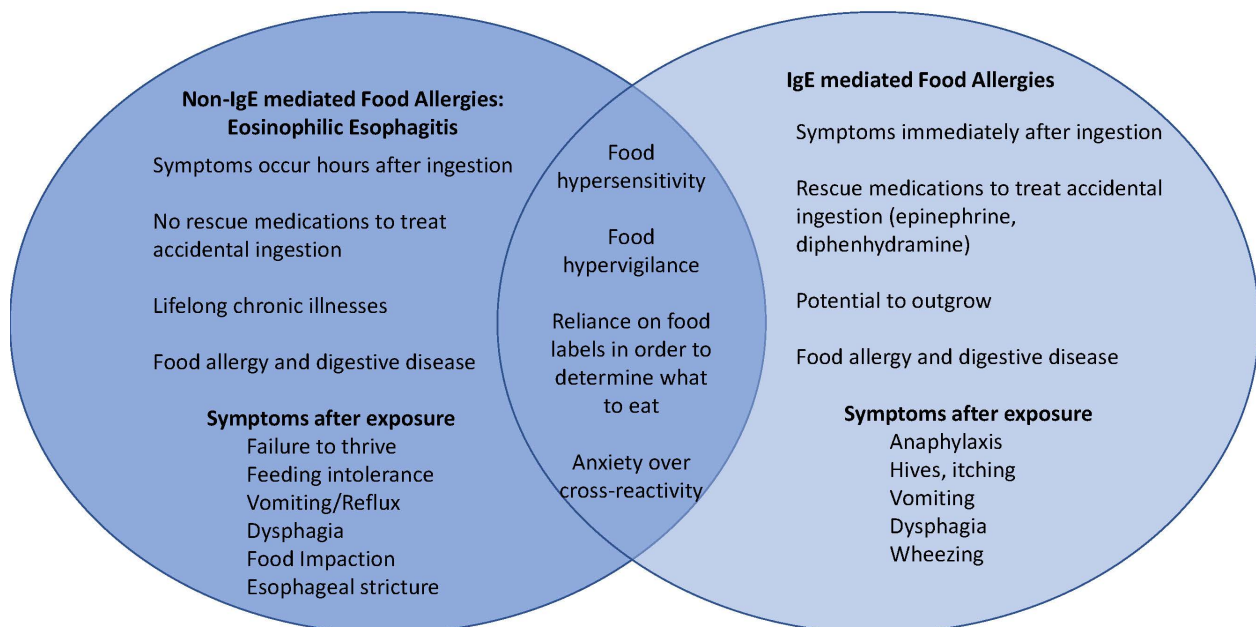
The Venn diagram below illustrates the key near-peer similarities between food allergies that are Non-IgE-Mediated Mechanisms with Celiac Disease (Gluten)/Eosinophilic Esophagitis and typical IgE-Mediated Mechanisms: potentially life-threatening, the only treatment is to strictly avoid the food allergen(s),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

¹¹ <https://farrp.unl.edu/IRChart>

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



Non-IgE Mediated Food Allergies: Eosinophilic Esophagitis (EoE) and IgE Mediated Food Allergies



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 and EoE are lifelong (until such time as a cure may be developed).¹²

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 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 and EoE 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 thoughts with you that Gluten should 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 and over 200,000 with EoE safe.

Thank you.

Sincerely,



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¹² 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.