CENTER FOR Science IN THE Public Interest

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 Rockville, MD 20852

Re: Notice of Request for Comments, Sesame as an Allergen in Foods (Docket No. FDA-2018-N-3809)

To Whom it May Concern:

The Center for Science in the Public Interest (CSPI) respectfully submits the following comments on the Food and Drug Administration's (FDA's) request for data and other information on sesame allergy in the United States.[1] CSPI is a non-profit consumer education and advocacy organization that has worked since 1971 to improve the public's health through better nutrition and safer food. The organization does not accept government or corporate donations and is supported by subscribers to its *Nutrition Action Healthletter*.

CSPI provides nutrition and food safety information directly to consumers and has long advocated for clear labeling and sensible regulation of allergens in food, including by pressing for the passage of the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) and the Food Safety Modernization Act of 2011 (FSMA), which strengthen requirements for allergen labeling in the United States. CSPI previously successfully petitioned the FDA to prevent allergic reactions by limiting the use of sulfites in foods[2] and by requiring labeling for cochineal extract and carmine in foods and cosmetics.[3]

We are pleased that the agency is considering the need for regulatory action on sesame because such action is essential to protect and promote the public health. In particular, we appreciate the recent statement by FDA Commissioner Scott Gottlieb announcing the current request for data as part of a new agency effort to consider sesame allergen labeling.[4] The commissioner rightly recognized that the prevalence of sesame allergy is "on

[1] Sesame as an allergen in foods. 83 Fed. Reg. 54,594 (Oct. 30, 2018).
[2] Molotsky I. U.S. issues ban on sulfites' use in certain foods. *New York Times*. July 9, 1986.
[3] Listing of color additives exempt from certification; food, drug, and cosmetic labeling: cochineal extract and carmine declaration. 74 Fed. Reg. 207 (January 5, 2009).
[4] Food and Drug Administration. *Statement from FDA Commissioner Scott Gottlieb, M.D., on the FDA's new consideration of labeling for sesame allergies*. October 29, 2018. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624484.htm.

par with allergies to soy and fish," two major allergens that must be labeled. We are also encouraged that the commissioner described the current request for information as a "first step" in a more complete process. We hope that the next step the agency takes occurs swiftly and results in the full and complete assurance that sesame will be labeled in the United States in the same manner as other major allergens.

With that in mind, we also must point out that this request for information is itself unnecessary as a first step toward sesame labeling, insofar as it may delay more decisive action by the agency. Such action is long overdue. CSPI and others previously submitted information to the FDA sufficient to support immediate action to require that sesame be labeled in foods. This information is available to the agency in our November 2014 petition (CSPI's Sesame Labeling Petition[5]) and comments on that docket, which we hereby fully incorporate by reference into these comments.

In the present comments, CSPI does not amend the request for a remedy that was contained in our original petition, which has been pending with the FDA for more than four years. Instead, we summarize the ample scientific evidence already provided in support of our Sesame Labeling Petition, describe in further detail the agency's legal authority to require sesame labeling, and analyze comments to the current sesame docket, which overwhelmingly support the need for sesame labeling.

We also encourage the FDA to keep open the current docket into the new year, as we expect additional scientific publications on sesame allergy to become available in the near future, including new nationwide estimates of the prevalence and severity of sesame allergy in adults.

I. Scientific Evidence for Sesame Labeling

It is estimated that sesame allergy affects more than 300,000 Americans. Sesame poses a public health concern similar to that from the eight "major" food allergens for which allergen labeling is federally required (milk, eggs, fin fish, shellfish, tree nuts, peanuts, wheat, and soybeans—commonly referred to as the "Big Eight").

While the presence of sesame must be labeled in the European Union, Australia and New Zealand, and Canada, it has been left out of the laws and regulations supporting allergen labeling in the United States. Unlike the Big Eight allergens, sesame may be concealed on food labels as a "spice" or "natural flavor," and both sesame and ingredients derived from it are sometimes declared only by use of an uncommon name (e.g., "benne seeds" or "tahini"). In addition, food manufacturers often fail to include sesame when developing controls for addressing allergen cross-contact risks, instead considering only risks for the Big Eight allergens.

[5] Requests that the FDA require sesame based ingredients to be listed by name (sesame) in the ingredient lists of all foods; and, add sesame to the FDA's list of allergens in Sec. 555.250 of the Statement of Policy for Labeling and Preventing Cross-contact of Common Food Allergens. www.regulations.gov. Docket Number FDA-2014-P-2035. https://www.regulations.gov/docket?D=FDA-2014-P-2035.

In 2014, CSPI, joined by a group of distinguished allergy experts and academics, filed the Sesame Labeling Petition, which asked the FDA to require sesame to be labeled and regulated in the same manner as the Big Eight.[6] As of this filing, that petition has garnered close to 800 comments, overwhelmingly in support of sesame labeling. Many of these comments include unique and personal stories describing severe reactions from sesame and the impact the condition has had on the authors' lives, as well as the lives of hundreds of thousands of American families.

In April 2018, CSPI organized a group of sesame-allergic families and their advocates to meet with Dr. Susan Mayne, Director of the FDA's Center for Food Safety and Applied Nutrition (CFSAN) and others from the FDA. The families shared stories of the serious effects of sesame exposure and of their difficulties in avoiding foods with sesame.[7] CSPI also submitted data on sesame allergy prevalence in the United States, as well as *Seeds of Change*,[8] a report that summarizes the latest scientific data on sesame allergy prevalence and severity and that documents that 14 out of 22 major food companies surveyed have already begun labeling for sesame.

CSPI also currently hosts an online survey tool as a resource for families with sesame allergy to submit reports of sesame reactions to the FDA.[9] Since launching the portal in October 2018, 321 reports of adverse reactions from sesame have been filed, with reaction dates from May 2008 to December 2018. Of these, 160 (50 percent) reported hospitalization or an emergency room visit and 119 (37 percent) reported treatment with epinephrine. There was one reported death, which occurred outside the United States.[10] Foods reported to have caused these reactions include bread, crackers, bagels, and other baked goods, as well as fried/flavored rice, hummus, tahini, and chicken nuggets. A total of 188 reaction reports (59 percent) indicated that the product was sold in a package (can, box, bottle, or bag) with a label that contained an ingredients list. Among these, 74 reports (39 percent) indicated that sesame was not declared in the ingredients or elsewhere on the product label. CSPI has submitted complete responses from the survey to the FDA's adverse event reporting database.

In addition to the evidence gathered and submitted to the FDA directly by CSPI, the need for sesame labeling is also supported by mounting evidence from the broader scientific community. In particular, in November 2016, the National Academies of Sciences, Engineering, and Medicine issued a report recognizing that "[t]he prevalence of sesame seed allergy in the United States appears to be equivalent to the existing eight priority foods or food groups recognized in the United States among children." The report urged

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[6] *Ibid.*
[7] 04.16.2018 CSPI and FARE memorandum of meeting. www.regulations.gov. Docket Number FDA-2014-P-2035. www.regulations.gov/document?D=FDA-2014-P-2035-0296.
[8] Center for Science in the Public Interest. *Seeds of Change*. Washington, DC: Center for Science in the Public Interest; April 2018. https://cspinet.org/sites/default/files/attachment/seeds-of-change-report.pdf.
[9] Sesame Reporting Form. Center for Science in the Public Interest. www.surveymonkey.com/r/sesame_reports.
[10] This submission was based on a media report: Matti, M. Natasha Inquest: Coroner Finds Inadequate Allergy Labeling Led to Teen's Death. AllergicLiving.com. www.allergicliving.com/2018/09/28/natasha-inquest-coroner-finds-inadequate-allergy-labeling-led-to-teens-death/.

that sesame be reconsidered for inclusion on the U.S. national priority allergens list.[11]

Most recently, new data from a nationwide survey conducted by Gupta et al. with responses from over 38,000 children, published in the journal *Pediatrics* in December 2018 (which CSPI has submitted to this docket separately), supports the conclusion that sesame allergy is similar in prevalence and severity to the Big Eight major allergens.[12] The survey results showed that 0.2 percent of children in the United states have sesame allergy. That ranks sesame 9th in prevalence among childhood food allergies, just behind soy (0.5 percent) and wheat (0.5 percent), two members of the Big Eight.

In addition, Gupta et al. reported that children with sesame allergy were more likely to report severe food allergy involving multiple organ systems or anaphylaxis than children with allergy to milk, one of the Big Eight.[13] In addition, two-thirds of children with sesame allergy were reported to have experienced a lifetime emergency department visit, a higher rate than that reported for any Big Eight allergen except soy, certain shellfish (lobster, crab), and fin fish.[14] Severe reactions were also more frequent: a third of sesame-allergic children experienced an emergency department visit related to a food allergy in the past year, a higher percentage than that for any other childhood allergy except fin fish, egg, and soy.[15]

We expect additional adult prevalence and severity data to be published soon, and plan to submit that publication to the agency when it becomes available. We are also including, as an Appendix to these comments, a bibliography with additional publications covering sesame allergy prevalence and severity, as well as two full articles establishing that sesame allergy threshold dose distribution is comparable to that of other food allergens.

This information clearly and unequivocally establishes the urgent need for immediate action to strengthen labeling requirements for sesame in order to protect and promote the public health.

II. FDA Authority for Allergen Labeling

The FDA may require sesame to be labeled as an ingredient by relying on its general labeling authority, FALCPA, FSMA, and the Food Code. Some of the actions that the FDA may take on sesame labeling would require rulemaking. Other actions, however, could be announced though guidance as a clarification of existing law and regulation.

Accordingly, we encourage the agency to consider the following measures, which together would bring sesame labeling into alignment with labeling requirements for other major

[11] Stallings VA, Oria MP, *et al*. Finding a path to safety in food allergy: assessment of the global burden, causes, prevention, management, and public policy. Washington, DC: National Academies Press; 2017.
[12] Gupta RS, Warren CM, Smith BM, *et al.* The public health impact of parent-reported childhood food allergies in the United States. *Pediatrics*. 2018;142(6):e20181235.
[13] *Ibid.* Table 3.
[14] *Ibid.*
[15] *Ibid.*

allergens:

Rulemaking:

- Promulgate regulations under FDCA 403(x) to require sesame to be disclosed when used as a spice or flavoring.
- Amend 21 C.F.R. § 101.4 to require that when a food allergen, including sesame or a derivative thereof, is declared in the ingredient statement, the common name for the food source be declared either in the ingredient name or in a parenthetical following the name (e.g., "benne (sesame seeds)," "tahini (sesame seed paste)," or "sesamol (from sesame seeds)").
- Amend 21 C.F.R. § 117.3 to define "Food allergen" as "a major food allergen as defined in section 201(gg) of the Federal Food, Drug, and Cosmetic Act, sesame, or other priority allergens identified by the FDA."

Guidance/Enforcement:

- Amend Compliance Policy Guide (CPG) 555.250 to list sesame expressly alongside other major allergens.
- Reiterate that the FDA may consider enforcement action if a food contains an undeclared allergenic ingredient that may render the food injurious to health, and take such action where warranted.

The Food Code:

- Amend the model food code to include sesame alongside other major allergens.

The authority for each of these actions is explained in further detail below.

i. General Labeling Authority

The FDA generally has the authority to prevent the interstate sale of foods bearing false or misleading labeling under FDCA Section 403(a) (*codified as* Section 343(a)), and to prevent the interstate sale of adulterated foods under Section 402(a) (*codified as* Section 342(a)). In addition, Section 403(i) (*codified as* Section 343(i)) requires that food manufacturers provide a list of ingredients by their common or usual name on the food labels.

The Section 403(i) ingredient list requirement generally applies to all ingredients added to foods, but contains an exception for ingredients added as spices, flavorings, and some colorings, which need not be separately identified. This exception allows ingredients derived from sesame and other non-Big Eight allergens to go undeclared when used for

flavoring or spice.[16]

Further instructions on ingredient naming are offered in regulation 21 C.F.R. § 101.4. For example, section 101.4(b)(14) requires that each individual oil ingredient be specifically listed by the common or usual name of its source, including fats and oils derived from allergenic food sources. Thus, "sesame oil" must be labeled as such, rather than under more generic and confusing names such as "oil" or "vegetable oil."[17]

Unfortunately, apart from oils and fats, section 101.4 does not specify that ingredients derived from an allergenic food source (e.g., pastes, powders, and extracts) must clearly declare that source using a standardized name. This allows ingredients that contain allergenic proteins to appear without clearly citing the source of the ingredient (e.g., "tahini" instead of "sesame seed paste" or "sesamolin" instead of "sesame seed extract"). Section 101.4 also fails to require a uniform common or usual name for each allergen. This allows allergenic ingredients to be listed under regional or foreign names (e.g., "benne," "gingelly," or "sim sim" rather than "sesame").

Prior to the passage of FALCPA, the FDA relied on its authorities under 403(a), 402(a), and 403(i) to strengthen food allergen labeling requirements. In a "Notice to Manufacturers" letter dated June 10, 1996, the agency relied on these authorities in offering advice to manufacturers on food allergen labeling.[18] In that letter, the agency indicated that it was "considering whether it is necessary to clarify its regulations to ensure that manufacturers fully understand the circumstances in which allergenic food ingredients must be declared."[19] The agency also made clear that manufacturers should take steps to eliminate cross-contact risks through adherence to current Good Manufacturing Practices (cGMPs).

The FDA further solidified this policy in August 2000, when it issued Compliance Policy Guide (CPG) Section 555.250, Statement of Policy for Labeling and Preventing Cross-contact of Common Food Allergens.[20] In that document, the agency made clear that improper allergen control practices "may be insanitary conditions that may render the food injurious to health and adulterate the product under Section 402(a)(4) of the FDCA."[21]

While that CPG 555.250 focused on the Big Eight major allergens that were subsequently included in FALCPA, the FDA also included allergens outside the Big Eight, stating that

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[16] The FDA has offered conflicting guidance on labeling for spices, indicating in a footnote to its guidance defining "spices," issued in 1980, that "[p]oppy seeds, sesame seeds, dried or dehydrated onions and garlic are not considered to be spices. When used as an ingredient in foods they should be declared on the label by common or usual names." Food and Drug Administration. Compliance Policy Guide 525.750 Spices – Definitions. Issued: 10/1/80. www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074468.htm. Yet the agency appears to have disregarded this definition in more recent guidance on Reference Amounts Customarily Consumed, listing "granulated garlic, granulated onion, garlic powder, onion powder," and "poppy seed, sesame seed, celery seed" as "examples of products" that fit into the product category "spices, herbs." Food and Drug Administration. Reference amounts customarily consumed: list of products for each product category: guidance for industry. February 2018. www.fda.gov/downloads/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm535370.pdf.

[17] 21. C.F.R. § 101.4(b)(14).

[18] Food and Drug Administration. Label declaration of allergenic substances in foods; notice to manufacturers. June 10, 1996. https://wayback.archive-it.org/7993/20170111004312/http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/ucm106546.htm.

[19] *Ibid.*

[20] Food and Drug Administration. Compliance Policy Guide Section (CPG) 555.250, Statement of Policy for Labeling and Preventing Cross-contact of Common Food Allergens. Issued: 04/19/2001. Updated: 11/29/2005. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-ice/documents/webcontent/ucm074552.pdf.

[21] *Ibid.*

"criteria for recommending legal action" included: "The food contains an undeclared allergenic ingredient, but the ingredient is not one of the eight (8) allergens listed in this guide."[22] The agency also stated in a footnote that it was still "exploring whether allergenic ingredients in spices, flavorings, or colors should be declared, 21 U.S.C. § 343(i) notwithstanding."[23]

The FDA can and should improve labeling for sesame by amending its regulations for declaring spices, flavorings, or colors, as it was considering doing for all food allergens in 1996 and 2000. Specifically, we encourage the FDA to amend 21 C.F.R. § 101.4 to require that when a food allergen, including sesame or a derivative thereof, is declared in the ingredient statement, the common name for the food source be declared either in the ingredient name or in a parenthetical following the name (e.g., "benne (sesame seeds)," "tahini (sesame seed paste)," or "sesamol (from sesame seeds)"). Such an amendment to regulations is authorized as a means of clarifying the "common or usual name" of foods under 21 U.S.C. § 343(i), and also under the agency's authority to prevent a food from being rendered injurious to health under Section 402(a) and to prevent false or misleading labeling under Section 403(a).

In addition, the FDA can and should protect consumers with sesame allergy by making clear that the cGMP requirements outlined in CPG 555.250 extend to sesame just as they do other major allergens.

Finally, the FDA can and should encourage food manufacturers to include other non-Big Eight allergens in their cGMP allergen programs by emphasizing the agency's longstanding position that any allergen that "may render the food injurious to health" may be considered an adulterant and render a food misbranded if undeclared in the ingredients list. Such a statement would be an affirmation of the agency's existing policy, as any allergen known to cause severe allergic reactions should be addressed as part of a manufacturer's cGMP program in accordance with CPG 555.250.

ii. FALCPA Authority

The FDA was still considering, but had not yet acted to require, stronger allergen labeling when Congress enacted FALCPA in 2004.[24] That law, which came into full effect in 2006, requires food manufacturers to label products that contain a "major food allergen" with the name of that allergen, either in the ingredients list or under a separate "contains" statement. Ingredients that are further processed from a food source must be followed by the name of that food source in parenthesis (e.g., "whey (milk)").

At the time of FALCPA's passage, scientific data on the prevalence and severity of sesame allergy were unavailable. FALCPA therefore defined "major food allergen" to include only

[22] *Ibid.*
[23] *Ibid.*
[24] Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA). Pub. L. No. 108-282, Title II. (2004).

the Big Eight allergens that had been identified by the FDA for special attention in CPG 555.250 and that were listed internationally as priority allergens for public health.

Yet Congress never intended that FALCPA restrict the FDA from identifying additional priority allergens in the future. Any such limitation would be contrary to the very purpose of FALCPA, which was to prevent allergic reactions in consumers through clear and informative labeling. Congress foresaw the need to extend the list of priority allergens beyond the Big Eight, and FALCPA therefore expressly authorized the FDA to prioritize additional allergens by adding Section 403(x) to the FDCA (*codified as* 21 U.S.C. § 343(x)). That section states:

> (x) Nonmajor food allergen labeling requirements
>
> Notwithstanding subsection (g), (i), or (k), or any other law, a spice, flavoring, coloring, or incidental additive that is, or that bears or contains, a food allergen (other than a major food allergen), as determined by the Secretary by regulation, shall be disclosed in a manner specified by the Secretary by regulation.

Section 403(x) both preserved and expanded the FDA's authority to require labeling for food allergens beyond the Big Eight. As explained in the Senate Report on FALCPA:[25]

> The legislation also adds a second misbranding provision to account for other food allergens. In particular, section 403(x) provides that FDA has the authority to require by regulation appropriate labeling of any spice, flavoring, coloring, or incidental additive ingredient that is, or includes as a constituent, a food allergen that is not a major food allergen. The committee does not intend the listing of all spices or flavorings in a product but intends that the Secretary will require the food allergen to be identified on the label in a manner consistent with this legislation. In addition, the legislation provides that the amendments made by it do not otherwise alter FDA's authority to require the labeling of other food allergens that are not major food allergens.

Similarly, the House Report also makes clear that Section 403(x) was intended to ensure that additional allergens identified by the FDA in the future not be concealed as "spices and flavorings":[26]

> New section 403(x) states that the exemption from current law food labeling requirements for spices, flavorings, colorings, or incidental additives does not apply in cases where these ingredients contain a food allergen that is not a major food allergen. In such a case, the food allergen shall be disclosed in a manner specified by the Secretary by

[25] S. Rep. No. 108-226, at 10 (2004).
[26] H.R. Rep. 108-608, at 17-18 (2004).

regulation.

Section 403(x) and its legislative history conclusively demonstrate that Congress authorized the FDA to extend FALCPA's allergen labeling requirements to new priority allergens beyond the Big Eight, using both 403(x) and the agency's pre-existing authority under 403(a), 402(a), and 403(i). Congress was concerned that the named "Big Eight" was not an exhaustive list of priority allergens, that dangerous allergens not on that list could remain undeclared, including by being hidden as spices and flavors, and that the FDA may have to use its authority as a public health agency to address this problem. That is the precise situation with which we grapple here.

Since the passage of FALCPA, the FDA has cited Section 403(x) as authority for new regulation only once, when it required a specific labeling declaration for carmine/cochineal, a color additive, in 2009 (an action also requested by CSPI through a Citizen Petition).[27] As the agency stated in the preamble to the final rule on carmine/cochineal, "[a]dditional legal authority for requiring disclosure of a coloring that is, or that bears or contains, a food allergen comes from section 403(x) of the [FDCA]. Under that section, a coloring determined by regulation to be, or to bear or contain, a food allergen must be disclosed in a manner specified by regulation."[28] In that instance, the agency did not require prevalence data, but instead acted "in response to reports of severe allergic reactions, including anaphylaxis, to cochineal extract and carmine-containing food and cosmetics."[29]

FALCPA's amendments to the FDCA provide the FDA with ample authority to require sesame labeling in this instance. We therefore reiterate the request in our 2014 petition to the FDA to immediately begin promulgating regulations under 21 U.S.C. § 343(x) to require that sesame be disclosed when used as a spice or natural flavoring.

iii. FSMA Authority

FALCPA did not modify the FDA's authority to require food manufacturers to address allergen cross-contact risks, nor did it require manufacturers to label for such risks through "may contain" or similar statements. However, changes to the cGMP regulations addressing allergen risks did come about as a result of the enactment of FSMA, which provided a new federal framework for regulating allergen hazards that occur in food manufacturing. Specifically, FSMA required food manufacturers to conduct a hazard analysis and implement preventive controls for reasonably foreseeable hazards, including food allergen hazards.[30]

As noted above, the FDA had already taken steps to make clear to food manufacturers that

[27] Listing of Color Additives Exempt from Certification; Food, Drug, and Cosmetic Labeling: Cochineal Extract and Carmine Declaration. 74 Fed. Reg. 207 (January 5, 2009).
[28] *Ibid.*
[29] *Ibid.*
[30] Food Safety Modernization Act (FSMA). Pub. L. No. 111-353, Sec 103 (2011).

allergen control is a necessary component of cGMP. In promulgating final rules under FSMA in 2014, the agency took the opportunity to codify these requirements more explicitly into its cGMP regulations. As the agency stated in the preamble to the rule, these updates "clarified FDA's long-standing position that the cGMPs address allergen cross-contact by making that explicit in the regulatory text."[31] In effect, the FSMA rule did not create new requirements, but rather codified into regulation elements of CPG 555.250.

In codifying these allergen requirements, the FDA for the first time provided a regulatory definition for the term "food allergen." Under 21 C.F.R. § 117.3, a "food allergen" was "a major food allergen as defined [in FALCPA]." This definition includes only the Big Eight. Yet the FDA did not retract CPG 555.250 when it promulgated the FSMA rule, nor did it reverse its position that any allergen that may render a food "injurious to health" which is not declared on the label can result in the food being adulterated or misbranded, justifying enforcement action by the agency.

Nothing now prevents the FDA from clarifying its cGMP requirements further by including sesame in the definition of "food allergen" in recognition of the fact that sesame can cause serious allergic reactions, thereby rendering a food injurious to health. The agency can do so by amending 21 C.F.R. § 117.3 to include sesame, as well as any other allergens it may identify as priority allergens in the future, under the definition of "food allergen."

We therefore request that the agency amend 21 C.F.R. § 117.3 to define "food allergen" as "a major food allergen as defined in section 201(gg) of the Federal Food, Drug, and Cosmetic Act, sesame, or other priority allergens identified by the FDA." Such changes could be combined in the same rulemaking with regulations requiring sesame labeling issued under 21 U.S.C. § 343(x).

Notably, these changes should have minimal cost for members of industry already carefully practicing cGMP, because they do no more than codify the FDA's longstanding position in CPG 555.250 that undeclared non-Big Eight allergens known to cause serious health risks may be considered adulterants. Many companies already recognize that sesame is a potential adulterant and therefore include it in their allergen programs. Unfortunately, many other companies still fail to recognize the obvious risks related to sesame, and this neglect has undoubtedly contributed to the high frequency of severe allergic reactions reported for people with sesame allergy.

Codifying sesame into 21 C.F.R. § 117.3 is therefore a critical step to ensuring that the remaining food companies that do not already control for sesame cross-contact risks come to recognize the need for this safety measure and include sesame in their allergen control programs.

[31] Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food; Final Rule. 80 Fed. Reg. 55,908, 55913 (September 17, 2015). www.gpo.gov/fdsys/pkg/FR-2015-09-17/pdf/2015-21920.pdf.

iv. The Food Code

The FDA is responsible for publishing the Food Code, a document that serves as a model for state and local government agencies and provides them with a scientifically sound technical and legal basis for regulating the retail and food service segments of the food industry (including restaurants, grocery stores, and institutions such as nursing homes).[32] The Food Code is updated, with input from the Conference for Food Protection, every four years. The most recent version was published in 2017.[33]

FALCPA directed the FDA to update the Food Code to include allergen requirements. These requirements, along with a definition of "major allergen," appeared in the Food Code for the first time in 2005.[34] The 2017 version of the code addresses allergen labeling on packaged foods sold at retail, training of restaurant staff, and avoidance of cross-contact risks.[35] However, as written, the Food Code limits these recommendations to the Big Eight major allergens. The FDA should extend the Food Code's model recommendations to include sesame.

While such a change would not be directly enforceable by the FDA, it would encourage state and local governments to include sesame as part of local allergen-related requirements. In addition, the courts will sometimes defer to the FDA in establishing reasonable standards of care for restaurant foods. For example, in 2016 a court looked to FDA rules in dismissing a case against restaurant chain Pret A Manger, which had been filed on July 5, 2016, by a customer who had reacted to a ready-made sandwich that had not included sesame in the ingredients list on its label.[36] The court reasoned in part that "[t]he FDA does not deem sesame to be a major food allergen and does not require food manufacturers or retailers to list it as an ingredient on a food label. Since sesame is not considered to be a major food allergen, it cannot be said that Pret A Manger misbranded or falsely labeled its sandwich."[37] Were the FDA to require sesame to be labeled as a major allergen, such cases may have a better chance in the future, prompting restaurants to exercise greater caution in controlling for and labeling this ingredient.

III. Responses to the FDA's Request for Information on Sesame Overwhelmingly Support the Need for Sesame Labeling

To date, over 8,700 comments have been submitted by the public in response to the FDA's request for information on sesame, including over 4,600 comments submitted as a batch by CSPI. The overwhelming majority of these comments—many of them from people who

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[32] Food and Drug Administration. FDA Food Code. Last Updated 12/03/2018. www.fda.gov/food/GuidanceRegulation/retailfoodprotection/foodcode/default.htm.
[33] *Ibid.*
[34] Food and Drug Administration. 2005 Food Code – Summary of Changes. https://wayback.archive-it.org/7993/20170404235517/https://www.fda.gov/Food/GuidanceRegulation/RetailFoodProtection/FoodCode/ucm124054.htm.
[35] Food and Drug Administration. Food Code. 2017. www.fda.gov/downloads/Food/GuidanceRegulation/RetailFoodProtection/FoodCode/UCM595140.pdf
[36] Matti M. Teen's tragedy 'devastating' news to man who sued Pret after sesame allergy reaction. *Allergic Living.* October 18, 2018. www.allergicliving.com/2018/10/18/teens-tragedy-devastating-news-to-man-who-sued-pret-after-sesame-allergy-reaction/.
[37] Matt v. Pret A Manger (USA) Ltd. 2018 NY Slip Op 30173 (January 31, 2018). https://law.justia.com/cases/new-york/other-courts/2018/2018-ny-slip-op-30173-u.html.

have been personally affected—support sesame labeling. In addition, the following groups have filed comments in support of sesame labeling:

Asthma and Allergy Foundation of America (AAFA)
Allergy and Asthma Network (AAN)
American Academy of Pediatrics (AAP)
American College of Allergy, Asthma, and Immunology (ACAAI)
American Partnership for Eosinophilic Disorders (APFED)
Campaign Urging Research for Eosinophilic Disease (CURED)
End Allergies Together (EAT)
Food Allergy and Anaphylaxis Connection Team (FAACT)
Food Allergy Research & Education (FARE)
FPIES Foundation
International FPIES Association

CSPI is aware of only one group—the Food Allergy Research and Resource Program (FARRP) at the University of Nebraska-Lincoln—that filed comments opposing sesame labeling. The FARRP is an industry-funded consortium whose mission is to provide the food industry with information, opinions, tools, and services related to allergenic and novel foods.

In its comment, the FARRP argues primarily that the FDA should not consider adding sesame (and by extension any other allergen) to the U.S. priority allergen list because no study of national food allergy prevalence exists that combine surveys with serum IgE measurements (blood tests), skin prick tests, and food challenges, ideally double-blind placebo-controlled challenges.[38]

Requiring such a study before protecting Americans from severe allergy risks would be both reckless and absurd. As FARRP admits, no such studies were required for the original U.S. major allergen list or the list of any other country. The obvious reason is that a study powered to detect national allergen prevalence using these methods would be prohibitively expensive.

The FARRP also carelessly encourages the FDA to adjust sesame prevalence numbers from the current best peer-reviewed estimates of 0.1 to 0.2 percent to a much lower 0.0016 to 0.0032 percent because "only 1.6 percent of children with self-reported food allergies would be confirmed by [double-blind placebo-controlled food challenge]."[39]

This poorly considered statement is based on data from the Food Allergy and Intolerance Research Study (FAIR), a population-based cohort study of challenge-confirmed food allergy prevalence conducted on the Isle of Wight.[40] It is worth pointing out that the FARRP made an arithmetic error in making its adjustment: the 1.6 percent figure was the percent

[38] Downs M, Kabourek J, Baumert J, Johnson P, Taylor S. Response to docket no. FDA-2018-N-3809. Sesame as an allergen in foods. Food Allergy Research & Resource Program of the University of Nebraska-Lincoln. Undated. https://www.regulations.gov/docket?D=FDA-2018-N-3809.
[39] *Ibid.* at 4.
[40] *Ibid.*

of *total subjects* (798) in that study, not the percent of "subjects with self-reported food allergy."[41] In addition, the low percent confirmed in that study must be interpreted with caution due to the low response rate (55 percent) and the fact that only 19 children (2 percent) underwent a confirmatory food challenge.[42]

The FARRP also inexplicably fails to mention the sesame allergy prevalence estimates from the FAIR Isle of Wight study, which are currently the only sesame allergy prevalence estimates confirmed by food challenge available worldwide. These estimates range from 0.1 percent to 0.73 percent prevalence, depending on the cohort being assessed, with the higher prevalence estimates coming from the cohorts with the higher response rate.[43,44,45] Such estimates are similar to or higher than the North American survey estimates reported by Gupta *et al* and others. If anything, such results suggest that prevalence estimates based on survey data might actually under-estimate the true prevalence of sesame allergy confirmed by food challenge, possibly due to the fact that such surveys may exclude numerous self-reports based on insufficient evidence.[46]

The FARRP also asserts, incorrectly and without citation, that "the prevalence of sesame in provoking severe allergic reactions is considerably lower than peanuts, tree nuts, milk, and eggs."[47] This statement is contradicted by the severity data published by Gupta *et al.*, described above, that show that severe sesame allergy is more prevalent in children than severe milk allergy, and that frequency of severe reactions is higher for sesame than for any Big Eight allergen except fin fish, egg, and soy.

Finally, FARRP argues that sesame should not be labeled because the prevalence of sesame allergy is lower than the prevalence of Molluscan shellfish[48] and the Big Eight allergens. Yet the difference between sesame (0.2 percent) and the lowest-prevalence members of the Big Eight (soy and wheat, at 0.5 percent) is unremarkable in comparison to the five-fold difference between members of the Big Eight (soy and wheat, at 0.5 percent, vs. peanut, at 2.2 percent).[49]

More importantly, we question whether relative prevalence should be the critical factor in requiring a common-sense declaration for an intentionally added ingredient that is documented to cause severe reactions and even death. The FDA certainly did not consider

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[41] Venter C, Pereira B, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. *Pediatr All Immunol.* 2006;17:356-363.
[42] *Ibid.*
[43] *Ibid.*
[44] Venter C, Pereira B, Voigt K, et al. Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. Allergy 2008;63(3):354-9.
[45] Venter C, Patil V, Grundy J, et al. Prevalence and cumulative incidence of food hypersensitivity in the first ten years of life. *Pediatr Allergy Immunol* 2016;27(5):452-8.
[46] For example, Gupta *et al.* (2018) screened out reported allergy where the report lacked a "convincing" symptom from a pre-defined list. The prevalence of "convincing" sesame allergy meeting these criteria in Gupta *et al.* was only 0.2 percent. By contrast, the raw parent-reported sesame allergy prevalence was a much higher value of 0.5 percent. Letter from Dr. Ruchi S. Gupta to the FDA sharing data on severity and prevalence of sesame allergy. April 2, 2018. www.regulations.gov/document?D=FDA-2014-P-2035-0259. Figure 3.
[47] Downs M, Kabourek J, Baumert J, Johnson P, Taylor S. Response to docket no. FDA-2018-N-3809. Sesame as an allergen in foods. Food Allergy Research & Resource Program of the University of Nebraska-Lincoln. Undated. https://www.regulations.gov/docket?D=FDA-2018-N-3809.
[48] While the FDA has not announced that it is considering requiring labeling for Molluscan shellfish, CSPI would support such a step should the evidence supporting such action prove as compelling as it is for sesame labeling.
[49] Gupta RS, Warren CM, Smith BM, *et al.* The public health impact of parent-reported childhood food allergies in the United States. *Pediatrics*. 2018;142(6):e20181235.

prevalence when requiring labeling for carmine/cochineal, but rather relied on reports of severe adverse reactions to justify that decision.[50]

Sesame allergy affects over 300,000 Americans, is severe in roughly 40 percent of children, and has been documented to lead to life-threatening reactions. The data supporting these assessments are similar to or higher in quality than that used to establish the original Big Eight labeling requirements and should be sufficient to support requiring labeling for sesame.

The FARRP also submitted, as part of its comment, data from survey responses by 53 members of the food industry.[51] Such data on industry practices are potentially useful in an area in which little public information is available. Yet the reliability of this survey is severely undermined by the fact that the FARRP comment otherwise reflects, at best, a lack of thoughtful consideration in drafting. The methodology for the FARRP survey has not been peer-reviewed and the response rate is low, particularly among non-FARRP members. We also question whether companies that do not declare sesame are always aware of the ingredients in their supply chains. Our concerns are only heightened by the fact that the FARRP felt the need to discard as unreliable 300 of the 330 products reported as containing undeclared sesame.

The FARRP uses the survey results to argue that levels of sesame protein from undeclared sesame oil used in flavors are too low to trigger an allergic reaction. Even assuming that these calculations are correct, the FARRP's analysis would only apply to oils used in flavors. Respondents also reported other undeclared sesame ingredients, including one spice manufacturer who indicated that "sesame seed and sesame seed extract were used at levels 40% and 6.1%, respectively, in seasoning blend formulations with only [sic] sometimes declaring sesame for the food industry customer."[52] Moreover, numerous adverse event reports submitted to the FDA by CSPI and others have documented serious reactions to undeclared sesame in FDA-regulated foods, demonstrating in the most direct possible way that undeclared sesame causes severe health risks, regardless of the amounts of sesame oil in flavors reported in the FARRP survey.

The FARRP survey also asked respondents to predict the potential costs of sesame labeling. It is striking that when asked whether adding sesame as a priority allergen would "present substantial challenges," three-quarters of industry respondents (74 percent) said that it would not.[53] In qualitative responses, many of the companies that did not expect substantial changes indicated that they already either label for sesame or do not include sesame in their products.

[50] Listing of Color Additives Exempt from Certification; Food, Drug, and Cosmetic Labeling: Cochineal Extract and Carmine Declaration. 74 Fed. Reg. 207 (January 5, 2009).
[51] Downs M, Kabourek J, Baumert J, Johnson P, Taylor S. Response to docket no. FDA-2018-N-3809. Sesame as an allergen in foods. Food Allergy Research & Resource Program of the University of Nebraska-Lincoln. Undated. https://www.regulations.gov/docket?D=FDA-2018-N-3809.
[52] Comment at page 9.
[53] Comment at page 14.

Of note, many of the companies projecting high costs pointed to concerns related to cGMP (e.g., scheduling controls for sesame, allergen changeovers, validation, and testing) rather than ingredient labeling. As we indicated in the previous section, undeclared sesame that is not in a spice or flavor is already considered an adulterant by the FDA to the extent that it renders a food injurious to health, and companies aware of this risk are already labeling for sesame. Nevertheless, we expect that any clarifications by the FDA are likely to enhance compliance and thereby lead more companies to include sesame in their allergen programs. The FDA would likely offer a period of time for companies to phase-in any such changes, minimizing the economic disruption to industry.

IV. Conclusion

We appreciate that the FDA is considering whether to take regulatory action on sesame. The need for sesame allergen labeling is urgent, with serious, sometimes life-threatening reactions occurring every day. Even when there is no reaction, the threat of one hangs over affected families as a constant presence, limiting their freedom and activities.

The FDA has long had sufficient scientific evidence to justify action on sesame. We urge the agency to do so now, as every moment of further delay unnecessarily jeopardizes the lives of Americans living with this dangerous allergy.

Appendix

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Sesame allergy threshold dose distribution

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Background: Sesame is a relevant food allergen in France. Compared to other allergens there is a lack of food challenge data and more data could help sesame allergy risk management. The aim of this study is to collect more sesame challenge data and investigate the most efficient food challenge method for future studies.
Method: Records of patients at University Hospital in Nancy (France) with objective symptoms to sesame challenges were collected and combined with previously published data. An estimation of the sesame allergy population threshold was calculated based on individual NOAELs and LOAELs. Clinical dosing schemes at Nancy were investigated to see if the optimal protocol for sesame is currently used.
Results: Fourteen patients (10 M/4 F, 22 ± 14.85 years old) with objective symptoms were added to previously published data making a total of 35 sesame allergic patients. The most sensitive patient reacted to the first dose at challenge of 1.02 mg sesame protein. The ED_{05} ranges between 1.2 and 4.0 mg of sesame protein (Log-Normal, Log-Logistic, and Weibull models) and the ED_{10} between 4.2 and 6.2 mg. The optimal food challenge dosing scheme for sesame follows semi-log dose increases from 0.3 to 3000 mg protein.
Conclusion: This article provides a valuable update to the existing clinical literature regarding sesame NOAELs and LOAELs. Establishment of a population threshold for sesame could help in increasing the credibility of precautionary labelling and decrease the costs associated with unexpected allergic reactions. Also, the use of an optimal dosing scheme would decrease time spent on diagnostic and thereafter on the economic burden of sesame allergy diagnosis.

1. Introduction

Sesame seed is a relevant food allergen in France and was responsible of 3% of reported life threatening allergic reactions to foods in France in 2002 (Moneret-Vautrin et al., 2005). This allergy appears early in life, does not resolve naturally with time, and tends to persist in 80% of cases (Cohen et al., 2007). Sesame is listed in the European Union (EU), Canada and Australia/New Zealand directives regarding mandatory allergen labelling (Gendel, 2012). Avoidance diet and treatment of acute emergencies represent the current management of sesame allergy. However, sesame seeds are difficult to control in food production equipment due to their particulate nature and electrostatic properties (Derby et al., 2005). Total avoidance diets by allergic individuals are difficult (Taylor et al., 1986). Unintentional cross contact of food allergens with other products on the production is a main concern for food industries, food legislators and patients. In order to warn allergic consumers of possible unintended presence of allergens in their products, food producers use precautionary labelling in addition to mandatory contains labelling. Due to inconsistencies in the application of precautionary labelling by the food industry, many products contain unnecessary precautionary labelling (Hefle et al., 2007). These unnecessary warnings make avoidance diets more restrictive and some allergic patients are beginning to ignore all these precautionary labelling labels (Hefle et al., 2007), a practice which poses a risk for allergic reactions. Removing unnecessary precautionary labelling would increase confidence in labels and potentially reduce the number of unexpected food allergic reactions. The amount of food required to cause a reaction is important for allergy

List of abbreviations: DBPCFC, Double Blind Placebo Controlled Food Challenge test; ED, Eliciting Dose; EU, European Union; LOAEL, Lowest Observed Adverse Effect Level; NOAEL, No Observed Adverse Effect Level.

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and allergen management. Knowing the individual minimum reactive doses as well as the amount of each product consumed would make it possible to manage the risk for the allergic population (Crevel et al., 2007).

Preventing accidental exposure to food allergens could decrease the economic burden of food allergy anaphylaxis. In 2007, the Allergy Vigilance Network in France defined anaphylaxis as a systemic reaction in two or more organ systems, a drop in blood pressure, or serious respiratory symptoms. They assessed the economic cost of anaphylaxis between January 2004 and June 2006 (Flabbee et al., 2008). The direct cost of each emergency visit due to anaphylaxis ranged from 75 Euros to 4445 Euros depending on the severity of the reaction and the treatment received by the patient. The most severe cases of anaphylaxis required additional hospitalisation which had added costs of 2115 Euros per day. These are the estimated costs for hospitalization and emergency visits which do not take into account the indirect costs of absenteeism, loss of productivity and annual consultation or further tests because of adverse reactions to foods. Currently for sesame and other allergens, University Hospital in Nancy (France), uses up to three progression challenges plus a placebo on four separate days to diagnose food allergies. Using the optimal dosing scheme for sesame in the food challenge test could decrease the cost of hospital stays during diagnosis. An optimal dosing scheme would cover the most sensitive patients with lowest doses and could provoke reaction in patients that react to higher doses also if the dose escalation is appropriately designed, as proposed by Klein Entink et al. (Klein Entink et al., 2014). The No Observed Adverse Effect Level (NOAEL) is defined as the largest amount of food that an individual can ingest without causing an adverse reaction. The Lowest Observed Adverse Effect Level (LOAEL) is the lowest dose of an allergen ingested that produces an adverse effect. The individual threshold dose lies between NOAEL and LOAEL. Using individual NOAELs and LOAELs, it is possible to statistically calculate threshold dose distributions for an overall population. International stakeholders, including the UK FSA and the US FDA, agreed that probabilistic modelling is the most favourable approach to use for allergen risk assessment (Madsen et al., 2009) (Gendel et al., 2008). Previous studies used this method for the determination of threshold levels for a number of food allergen (Taylor et al., 2014) (Bindslev-Jensen et al., 2002) (Taylor et al., 2009). Data for sesame in these papers were limited to 21 patients from four different studies (Kanny et al., 1996) (Kolopp-Sarda et al., 1997) (Morisset et al., 2003) (Leduc et al., 2006) and more data could strengthen current modelling distributions for the sesame allergic population.

This study aimed to determine NOAELs and LOAELs for additional sesame allergic individuals and update the population threshold estimate for sesame. The current study combines new patients and data retrieved from previously published clinical data. Knowing the population threshold distribution for sesame could help in establishing reference doses for sesame which gives more guidance for all food allergy stakeholders when applying precautionary labelling. Furthermore, the clinical dosing schemes used were evaluated to investigate if the optimal protocol for sesame is currently implemented in clinical practice.

2. Material and methods

The study population consisted of 14 patients who had positive food challenge tests for sesame at University Hospital Nancy (France) between 2006 and 2013. Patients were included even if they had a history of severe reactions. Medical records were retrospectively consulted for information on age, sex, personal and family history and for other allergies, skin prick tests, specific IgE values and double blind placebo control food challenge (DBPCFC) tests for sesame. An informed written consent form was signed before the beginning of the protocol.

DBPCFC tests were performed according to the consensus protocol for the determination of the threshold doses for allergenic foods (Taylor et al., 2004). Patients underwent DBPCFC with crushed sesame seeds using stewed apple as a vehicle and stewed apple without sesame as a placebo. Sesame seeds were crushed and mixed with stewed apple. Doses were given cold and patients wore a nose clip to decrease organoleptic perception. Placebo consisted of stewed apple with crushed popcorn to mimic the texture of sesame mix with the vehicle. Progressive dosing schemes were spread over 3 days (plus a 4th placebo day) and ranged from 1 to 7010 mg of crushed sesame seeds (equivalent to 0.17–1200 mg of sesame proteins). Dosing schemes were adjusted depending on the patient's clinical history and severity of prior reactions. An interval of 15 min was observed between two doses. The challenge ended only when the patient experienced objective symptoms or when the highest dose of the challenge was achieved (in our case 7010 mg of sesame or 1200 mg of sesame protein). Objective symptoms included diarrhea, vomiting, conjunctivitis, urticaria, lip and throat swelling, bronchoconstriction, wheezing, angioedema, etc. Abdominal pain was considered as an objective symptom in children who didn't have symptoms with placebo food challenge (Taylor et al., 2010). Symptoms were graded according to the score of Astier et al. (Astier et al., 2006). This score was adapted by adding laryngeal pruritis to grade 1. Patients were asked to stop antihistamines one week before the challenge; beta antagonists and corticosteroids were stopped 24 h before the DBPCFC. Both discrete and cumulative NOAELs and LOAELs were recorded for each patient. These values were expressed in mg of total protein from sesame seed, which accounts for 17% of sesame seeds content (USDA, 2014).

Sesame NOAELs and LOAELs were combined with previously published data (Taylor et al., 2014). Data from twenty-one patients were used for the determination of the VITAL reference dose for sesame and came from 4 different studies previously published by Nancy research teams (Kanny et al., 1996) (Kolopp-Sarda et al., 1997) (Morisset et al., 2003) (Leduc et al., 2006).

Population threshold distributions were determined using the method proposed by Taylor et al. (Taylor et al., 2009). NOAELs and LOAELs were analyzed using an Interval-Censoring Survival Analysis (ICSA) approach. Statistics were performed in SAS v9.3 (SAS Research Institute) using the LIFEREG procedure. The (ED_{05}) or the eliciting dose that is predicted to provoke reaction in 5% of the population and the (ED_{10}) that could trigger reaction in 10% of the population (ED_{10})were estimated using the Log-Normal, Log-Logistic and Weibull parametric models.

We compared the three dosing schemes used for the diagnosis of sesame allergy by University Hospital in Nancy (Taylor et al., 2010), with the dosing schemes recommended by EuroPrevall (Sampson et al., 2012). The first Nancy dosage progression had a cumulative dose of 44.4 mg of sesame (7.5 mg sesame protein); the second Nancy dosage progression had a cumulative dose of 965 mg of sesame (164 mg sesame protein) and the third Nancy dosage progression with a cumulative of 7010 mg of sesame (1200 mg sesame protein). The discrete dosing scheme used by EuroPrevall was the same across all foods challenged: 0.003 mg, 0.03 mg, 0.3 mg, 3 mg, 30 mg, 100 mg, 300 mg, 1000 mg and 3000 mg food protein (cumulative dose of 4333.333 mg of protein).

3. Results

Fourteen new patients (10 M/4 F, 22 ± 14.85 years old) with objective symptoms during DBPCFC to sesame were considered for this study (Table 1). Patients 1 and 7 had a history related directly to sesame ingestion and/or manipulation. The 12 other patients had

Table 1
Clinical characteristics, symptoms and threshold doses under DBPCFC for sesame allergic individuals at the Nancy University Hospital in France from 2006 to 2013.

Subject	Age (years)	Gender	Symptoms (grade according to score Astier)[a]	mg protein	
				NOAEL[b]	LOAEL[c]
				Discrete (cumulative)	Discrete (cumulative)
1	29	m	Itching at the scalp and erythema behind the ears (1)	25.5 (36.55)	48.45 (85.00)
2	14	m	Laryngeal pruritis (1)	5.10 (7.48)	R-Cen[d]
3	9	f	Abdominal pain, urticaria (3)	8.50 (11.05)	R-Cen
4	66	m	Urticaria (hands, legs, behind ears) (1)	2.55 (2.55)	8.5 (11.05)
5	11	f	Abdominal pain (1)	595.00 (1190.00)	R-Cen
6	13	m	Abdominal pain, pallor, conjunctival erythema, pruritis in the ear canals, two urticarial papules on the dace (3)	8.50 (11.05)	25.50 (36.55)
7	38	m	Itching at the scalp, legs and hands (1)	850.00 (1207.00)	R-Cen
8	12	f	Erythema, abdominal pain, congested nose (3)	25.50 (36.55)	48.45 (85.00)
9	18	m	Conjunctival erythema of left eye (1)	11.05 (11.05)	25.50 (36.55)
10	18	m	Pruritis, facial urticaria tingling of the mouth (1)	L-Cen[e]	170.00 (170.00)
11	25	f	Pharyngeal tingling, chest tightness (1)	119.00 (164.05)	R-Cen
12	22	m	Abdominal pain and wheezing (1)	0.85 (0.85)	1.70 (2.55)
13	18	m	Wheezing with drop of peak expiratory flow of 17% (2)	85.00 (85.00)	255.00 (340.00)
14	16	m	Labial erythema, pruritis and abdominal pain (1)	34.00 (45.05)	119.00 (164.05)

[a] Astier score: a severity grading score that goes from 0 to 5.[21].
[b] NOAEL: No Observed Adverse Effect Level.
[c] LOAEL: Lowest Observed Adverse Effect Level.
[d] R-Cen: Individual who did not objectively react to the highest dose of the progressive dosing scheme but is believed to be allergic to sesame by strong clinical history.This individual would have an established NOAEL but would not have a defined LOAEL.
[e] L-Cen: Individual reacted to the first dose of the progressive dosing scheme and thus does not have an established NOAEL but does have a determined LOAEL.

Table 2
Sesame threshold data from 4 published studies plus unpublished clinical threshold data.

Study	Total number with objective symptoms	Population	Lowest LOAELS (mg of protein)	Highest LOAELS (mg of protein)
Kanny et al. (1996)	7	6 adults 1 children	30.78	3078
Kolopp-Sarda et al. (1997)	1	Age not reported	1208.7	
Morisset et al. (2003)	1	Age not reported	5.1	
Leduc et al. (2006)	12	7 adults 5 children	1.02	1190
New patients	14	9 adults 5 children	2.55	340
Total	35	22 adults 11 children 2 unknown	1.02	3078

received diagnostic DBPCFC tests after identification of sensitization to sesame by skin prick tests and/or serum IgE analysis. Patients had past histories of allergic symptoms of grade 4 in 1 patient, grade 3 in 8 patients, grade 2 in 4 patients and grade 1 in 1 patient upon consumption of foods that could contain sesame.

The most sensitive patient had a discrete NOAEL of 0.85 mg sesame protein and a cumulative NOAEL of 0.85 mg sesame protein and a discrete LOAEL of 1.70 mg of sesame protein and a cumulative LOAEL of 2.55 mg sesame protein; and experienced abdominal pain and wheezing (Table 1, patient 12). During the DBPCFC tests, 10 (71%) patients had grade 1 symptoms according to score Astier (Astier et al., 2006), 1 patient (7%) had grade 2 symptoms and 3 patients (21%) had grade 3 symptoms (Table 1).

The combination of previously published data (Appendix 1) and new patients increase the population analysis to a total of 35 sesame allergic NOAELs and LOAELs (Table 2). The most sensitive patient (out of all 35 patients) reacted to the first dose at challenge of 1.02 mg sesame protein with generalized pruritis and erythema on the neck (Leduc et al., 2006, patient 20).

Eliciting doses, expressed in mg of sesame protein, were extrapolated from the Log-Normal, Log-logistic and Weibull probabilistic distribution models that were fitted to the clinical threshold data. The cumulative ED_{05} by the three distributions was 1.0–2.4 mg sesame protein. The cumulative ED_{10} was calculated to be 4.2–6.2 mg sesame protein (Table 3).

The evaluation of sesame dosing schemes showed that the normal EuroPrevall scheme could cover all the sesame doses and add a higher dose when compared to the current protocol used by University Hospital Nancy (France). Based on the 35 available sesame patients, omitting the first two doses of the EuroPrevall scheme would not significantly alter the results of clinical challenges with sesame or the severity of the reactions at the first dose. The modified EuroPrevall dosing scheme for sesame would be the following: 0.3 mg, 3 mg, 30 mg, 100 mg, 300 mg, 1000 mg and 3000 mg of sesame protein.

Table 3
Doses of sesame protein predicted to cause a reaction in 5% (ED_{05}) and in 10% of sesame allergic population (ED_{10})*.

	Cumulative ED_{05} (mg sesame protein)	95% CI	Cumulative ED_{10} (mg sesame protein)	95% CI
Log- Normal	2.4	0.6, 9.6	5.9	1.8, 19.4
Log- Logistic	2.1	0.4, 10.4	6.2	1.7, 23.1
Weibull	1.0	0.1, 8.1	4.2	0.8, 22.6

*Cumulative Eliciting doses were calculated using Interval Censoring Survival Analysis and were fitted to the Log-Logistic, Log-Normal, and Weibull probability distribution models. All doses were calculated in mg sesame protein.

4. Discussion

This article provides a valuable update to the existing clinical literature regarding NOAELs and LOAELs of sesame allergic individuals. The fourteen new patients in this study were collected from low-dose oral challenges conducted for diagnostic purposes and patients were not excluded on the basis of severity of previous reactions. However, all patients' data used for the determination of sesame threshold come from University Hospital Nancy (France). More data from other hospitals and geographical regions would help confirm these initial findings.

The unintended presence of food allergens in products, despite best practices to minimize cross-contact, forces the food industry to use precautionary labelling as an attempt to warn food allergic consumers of the potential presence of food allergens. The overuse of these warning labels confuses allergic consumers and may push them to take risks by ignoring precautionary labelling and buying potentially hazardous products. Population threshold estimations could help in organizing and harmonizing the application of precautionary labelling. The population threshold is defined as the amount of food required to cause a reaction in a very sensitive population or in a small percentage of this population (ED_p; Eliciting Dose and p for the percentage of population). The first population threshold distribution for sesame was reported by Taylor et al., 2014 and contained 21 individuals. The updated sesame threshold distribution was slightly more sensitive but not in a statistically significant fashion. The distributions of each allergen could be compared among food allergens and therefore give an idea about their potency. Comparison of the updated sesame distribution with other major food allergens (Taylor et al., 2014) shows that sesame has comparable potency with peanut and milk. It seems that the sesame allergic population may be less sensitive than the egg and more sensitive than the hazelnut allergic populations but more data is needed to statistically confirm these initial findings (Fig. 1). In terms of practical daily life, a single sesame seed weighs 3.2 mg (0.544 mg of sesame protein). The lowest LOAEL in study ranges between 1.0 and 2.4 mg of sesame protein. Calculated in seeds of sesame, the threshold dose of the most sensitive patient in this study would range between 2 and 4.4 sesame seeds.

Reference doses used by food industries in the risk assessment of unintended presence of food allergens are based on estimations of population thresholds (Taylor et al., 2014). Precautionary labelling would only be placed on products where their presence was found needed after a thorough risk assessment. This risk assessment would help give credibility to precautionary labelling. It is also very important to establish effective communication between food industry, clinicians and consumers about the use of risk assessment. Having a risk assessment program based on values derived from population thresholds would give food legislators assurance to use this data and method to make informed public health decisions.

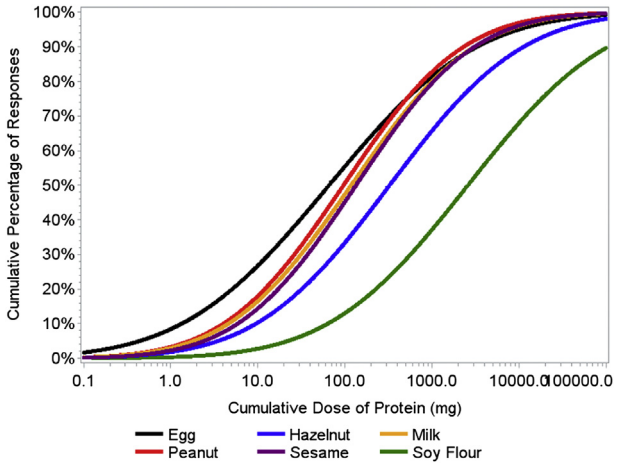

Fig. 1. Sesame probability distribution model compared to the Taylor et al., 2014 predicted probability models of peanut, milk, egg and hazelnut. All allergens are modelled with the Log-Normal distribution.

Prior to implementation of mandatory allergen labelling for sesame, a questionnaire in the UK showed that 17% of sesame self-reported allergic patients developed life-threatening symptoms and 91% of total reactions were to foods that contain sesame as an obvious ingredient (Derby et al., 2005). After the change in ingredient labelling requirements, unexpected reactions to allergens still occur on occasion when consuming pre-packaged foods. A number of allergic reactions are due to consumers ignoring precautionary labelling on these foods (Hefle et al., 2007). Preventing accidental exposures to allergens is a top priority for all allergen stakeholders, including patients, clinicians, food manufacturers, retailers, caterers and regulators (Hattersley et al., 2014). A systematic, scientific application of precautionary labelling could increase credibility of the label and trust of the allergic consumer. Proper communication would allow allergic patients to make more informed food choices. If they know their individual threshold level, allergic consumers would better understand the risk of reactions when exposed to allergens. Furthermore, there needs to be a priority and/or heavy emphasis on threshold education for patients in order to fully understand thresholds and their implications in daily life. Soller et al. showed that food challenge tests had a positive effect on the quality of life of allergic patients (Soller et al., 2014). It is believed that knowing their individuals threshold doses could improve their quality of life and day to day allergy management.

Finally, creating the proper optimal dosing scheme could decrease the economic burden of sesame allergy diagnosis. The current protocol in University Hospital in Nancy (France) is a progressive three day challenge. The modified EuroPrevall dosing scheme for sesame may be the optimal protocol to use in terms of cost effectiveness for the patient and for the hospital. It accounts for 7 progressive doses (0.3–3000 mg sesame protein) that can be given to the patient on a single day. Therefore, food challenge test in Nancy would be done in two days instead of a week and minimize the costs to the patient and to the hospital. The lowest doses cover the very sensitive sesame allergic population, but the scheme also covers the entire range of sesame reactors in a semi-log fashion and provides adequate information for interval censoring analysis (Klein Entink et al., 2014). The semi-log dose schemes have been used regularly and showed that it has high degrees of safety (Sampson et al., 2012). Additionally, this protocol could have possibly elicited objective symptoms in patients that do not react in the current sesame challenge protocol and provided more valuable information. The dosing protocol that we proposed for future sesame threshold studies or diagnostic challenges is based on a modified version of the dosing scheme used in the EuroPrevall threshold studies which covers a wide dosing range up to a final discrete dose of 3000 mg protein and is supported by a high level of consensus within the European Union and elsewhere. Our proposed dosing scheme includes a slight modification based on our analysis of the 35 sesame allergic patients reported in our current study. This dosing scheme would be useful for evaluating objective symptoms in patients reacting to low doses of sesame protein as well as those that react to high doses of sesame protein (3000 mg of sesame protein or 17647 mg of sesame seed).

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.05.011.

Appendix 1. Individual sesame threshold data retrieved from previously published data.

Study	Subject	Age (years)	Gender		mg of sesame protein	
				Symptoms	NOAEL[a] discrete (cumulative)	LOAEL[b] discrete (cumulative)
Leduc et al. (2006)	2	63	f	Systemic reaction	34 (45.05)	119 (164.05)
Leduc et al. (2006)	4	44	m	Flush facial eythema	8.5 (11.05)	34 (45.05)
Leduc et al. (2006)	6	33	m	Urticaria	340 (510.00)	850 (1190.00)
Leduc et al. (2006)	7	23	m	Urticaria,angioedema	8.5 (11.05)	34 (45.05)
Leduc et al. (2006)	8	25	f	Erythema, abdominal pain	34 (45.05)	119 (164.05)
Leduc et al. (2006)	10	17	f	Urticaria	34 (45.05)	119 (164.05)
Leduc et al. (2006)	12	6	m	Abdominal pain, cough, wheezing	340 (510.00)	850 (1190.00)
Leduc et al. (2006)	13	36	m	Generalized pruritis, erythema	340 (510.00)	850 (1190.00)
Leduc et al. (2006)	14	3	f	Exacerbation of atopic dermatitis	34 (45.05)	119 (164.05)
Leduc et al. (2006)	18	10	f	Urticaria, wheezing, vomiting	34 (45.05)	119 (164.05)
Leduc et al. (2006)	20	47	m	Generalized pruritis, erythema on the neck	L-Cen[c]	1.02 (1.02)
Leduc et al. (2006)	21	11	m	Asthma	170 (170)	340 (510)
Morisset et al. (2003)	1			N/A	1.7 (2.55)	2.55 (5.1)
Kolopp-Sarda et al. (1997)	4			Urticaria	255 (358.7)	850 (1208.7)
Kanny et al. (1996)	1	51		Abdominal pain at 1,5 h	2462.4 (3078)	R-Cen[d]
Kanny et al. (1996)	3	43		Anaphylactic shock	461.7 (615.6)	2462.4 (3078)
Kanny et al. (1996)	4	18	m	Urticaria and pharyngeal itching	L-Cen	30.78 (30.78)
Kanny et al. (1996)	5	35	m	Urticaria	461.7 (615.6)	1539 (2154.6)
Kanny et al. (1996)	6	33		Urticaria and itchy hands	461.7 (615.6)	1539 (2154.6)
Kanny et al. (1996)	8	4		Abdominal pain, conjunctivitis, eczema	461.7 (615.6)	1539 (2154.6)
Kanny et al. (1996)	9	23		Skin rash, asthma	461.7 (615.6)	2462.4 (3078)

[a] NOAEL: No Observed Adverse Effect Level.
[b] LOAEL: Lowest Observed Adverse Effect Level.
[c] L-Cen: Individual reacted to the first dose of the progressive dosing scheme and thus does not have an established NOAEL but does have a determined LOAEL.
[d] R-Cen: Individual who did not objectively react to the highest dose of the progressive dosing scheme but is believed to be allergic to sesame by strong clinical history. This individual would have an established NOAEL but would not have a defined LOAEL.

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Eliciting Dose and Safety Outcomes From a Large Dataset of Standardized Multiple Food Challenges

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Background: Food allergy prevalence has continued to rise over the past decade. While studies have reported threshold doses for multiple foods, large-scale multi-food allergen studies are lacking. Our goal was to identify threshold dose distributions and predictors of severe reactions during blinded oral food challenges (OFCs) in multi-food allergic patients.

Methods: A retrospective chart review was performed on all Stanford-initiated clinical protocols involving standardized screening OFCs to any of 11 food allergens at 7 sites. Interval-censoring survival analysis was used to calculate eliciting dose (ED) curves for each food. Changes in severity and ED were also analyzed among participants who had repeated challenges to the same food.

Results: Of 428 participants, 410 (96%) had at least one positive challenge (1445 standardized OFCs with 1054 total positive challenges). Participants undergoing peanut challenges had the highest ED_{50} (29.9 mg), while those challenged with egg or pistachio had the lowest (7.07 or 1.7 mg, respectively). The most common adverse event was skin related (54%), followed by gastrointestinal (GI) events (33%). A history of asthma was associated with a significantly higher risk of a severe reaction (hazard ratio [HR]: 2.37, 95% confidence interval [CI]: 1.36, 4.13). Higher values of allergen-specific IgE (sIgE) and sIgE to total IgE ratio (sIgEr) were also associated with higher risk of a severe reaction (1.49 [1.19, 1.85] and 1.84 [1.30, 2.59], respectively). Participants undergoing cashew, peanut, pecan, sesame, and walnut challenges had

more severe reactions as ED increased. In participants who underwent repeat challenges, the ED did not change ($p = 0.66$), but reactions were more severe ($p = 0.02$).

Conclusions: Participants with a history of asthma, high sIgEr, and/or high values of sIgE were found to be at higher risk for severe reactions during food challenges. These findings may help to optimize food challenge dosing schemes in multi-food allergic, atopic patients, specifically at lower doses where the majority of reactions occur.

Trials Registration Number: ClinicalTrials. gov number NCT03539692; https://clinicaltrials.gov/ct2/show/NCT03539692.

Keywords: oral food challenge, adverse events, dose curves, food allergy, safety outcome

INTRODUCTION

The prevalence of food allergies has continued to rise over the past decade and has become a significant health issue (1). Food allergies have become more common, and now affect 6–11% of the population in the United States, Canada, Australia, and Europe (2–8). Among children, 40% are affected by two or more food allergies (9). The diagnosis of food allergies imposes a significant burden on patients and their families and leads to a decreased quality of life due to dietary restrictions, increased anxiety, and social limitations (10). In recent years, in the US, the number of emergency room visits for food-induced anaphylaxis has risen to ∼200,000/year and continues to rise (11, 12).

The double-blind placebo-controlled food challenge (DBPCFC) is the gold standard method to diagnose food allergies. Recent studies have focused on comparing the utility of other clinical factors to be able to predict food challenge outcomes (13) and to understand the role of allergen-specific IgE (sIgE) and skin prick tests (SPTs) (14). However, there have been few comparisons of multiple DBPCFCs performed across a large population in which the challenges were done with the same standardized method. In a prior publication from our group (15), we demonstrated the presence of multiple food allergies in many individuals. Our sites perform clinical trials in food allergy and as such, a large number of DBPCFCs are conducted in a medical facility with trained personnel using the same doses and time intervals in a food challenge. Sometimes participants undergo repeat food challenges (without interim intervention) to the same allergen for qualification into clinical trials. Therefore, the objective of this research was to test whether food challenge reactions, if repeated over time, differed by severity, by eliciting dose (ED), or by organ system involvement. This was determined according to the type or dose of food allergen (16, 17). Another objective was to assess whether certain food allergens were associated with a certain type of reaction (i.e. a gastrointestinal (GI) allergic reaction vs. a skin allergic reaction).

MATERIALS AND METHODS

Oral Food Challenges (OFCs)

From September 2010 to March 2016, participants with suspected food allergy were recruited to undergo standardized food challenges to at least 500 mg of cumulative food protein to each of their allergens as part of screening for clinical trial enrollment. The low cutoff of 500 mg of food protein was chosen as these subjects had a high likelihood of exhibiting an allergic reaction. The precise amounts of commercially available, FDA standardized and validated GMP-grade protein were quantified based on protein gels, prepared and weighed out in our GMP facility, and distributed to other sites under a clinical trial agreement that ensured consistency in challenge material from batch to batch and between sites. Patients with a prior history of food-allergy reaction requiring intubation or eliciting hypotension were excluded, while patients with previous reactions to food requiring epinephrine for other severe symptoms were eligible. During the initial screening visit before multiple studies, SPT and IgE testing were performed at the Center for some trials, whereas, for others, results from prior testing at a physician's office were included. SPT consisted of a positive histamine control, a negative saline control (both from Hollister-Stier) and allergen extracts from Greer. SPTs were performed on the volar surface of the forearm or back after application of the respective allergen solution. Mean wheal diameter was measured after 20 min. Allergen-specific IgE levels were measured by ImmunoCAP fluorescence enzyme immunoassay.

One thousand four hundred and forty-five DBPCFCs were performed using standardized methodology according to validated guidelines (18–20). The same DBPCFC methods and doses were used across the Sean N. Parker Center for Allergy and Asthma Research at Stanford University, Cincinnati Children's Medical Center, Robert H. Lurie Children's Hospital of Chicago, Children's Hospital of Philadelphia, Virginia Mason Medical Center, Seattle Children's Hospital, Icahn School of Medicine at Mount Sinai, and Children's Hospital Los Angeles. All personnel were trained using procedures as per the protocol. Each challenge consisted of several escalating doses of the food protein in flour form concealed in an appropriate vehicle, such as applesauce or pudding, ingested by the participant every 15 min as tolerated. Challenges to almond, cashew, egg, hazelnut, milk, peanut, pecan, pistachio, sesame, walnut, and wheat were included in the analyses. Typically challenges started with as small as 1 mg (for pistachio), then 2, 5, 20, 50, 100, 100, 100, 123 (for pistachio), or 124 mg. Patients challenged with pistachio were individuals

with a known cashew allergy, and, as such, pistachio challenges were started at 1 mg due to concerns for safety. All allergen doses indicate mg of food protein. Those participants with positive DBPCFCs to placebo (oat) were excluded. A subset of patients performed repeat challenges to the same food in the course of screening for multiple trials. Vital signs and pertinent physical examinations were repeated every 15 min, or more frequently during the challenge, at the discretion of the clinician. Reaction types and severities were determined according to modified Bock criteria (18) and Common Terminology Criteria for Adverse Events (CTCAE v 4.03). Some studies recorded symptoms in CTCAE criteria and some with modified Bock. Our ranking system was based on Bock and the CTCAE was converted to Bock grading by allergists on our team. All objective and subjective symptoms were recorded and ranked against one another in order of severity by onsite physicians based on their clinical judgment. Subjective symptoms included abdominal pain, oropharyngeal itching, nausea, or pruritus. Objective adverse symptoms were regarded as more severe than subjective symptoms of the same grade and this was taken into consideration when ranking symptoms in **Table 1**. Participants tolerating at least 500 mg cumulative dose during the challenge were considered to be negative responders for the purposes of this analysis. All aspects of the studies from which data was obtained were authorized by the IRB.

TABLE 1 | Ranked adverse events by severity.

Symptom	Rank
Mild pruritus	1
Moderate pruritus	2
Mild nasal itching	3
Moderate nasal itching	4
Severe nasal itching	5
Mild nausea	6
Moderate nausea	7
Severe nausea	8
Mild Ab pain	9
Moderate Ab pain	10
Mild rhinorrhea	11
Mild nasal congestion	12
Moderate rhinorrhea	13
Mild sneezing	14
Moderate nasal congestion	15
Mild rash	16
Mild urticaria	17
Moderate sneezing	18
Mild angioedema	19
Severe rhinorrhea	20
Severe nasal congestion	21
Mild cough	22
Severe sneezing	23
Mild emesis	24
Severe Ab pain	25
Severe pruritus	26
Moderate rash	27
Moderate emesis	28
Moderate angioedema	29
Moderate cough	30
Moderate urticaria	31
severe rash	32
Severe urticaria	33
severe emesis	34
Severe angioedema	35
Severe cough	36
Mild airway obstruction	37
Moderate airway obstruction	38
Severe airway obstruction	39
Mild wheezing	40
Moderate wheezing	41
Severe wheezing	42
Mild cardio	43
Moderate cardio	44
Severe cardio	45

Higher ranking indicates more severe symptoms.

Data Management

Any value of sIgE greater than 100 IU/L was truncated to 101 for statistical analysis. Only SPT and/or sIgE that were collected within 12 months of the OFC were included in the analysis. If a subject had more than one value for SPT or sIgE, then the value obtained closest to the challenge was used (14). Negative control SPTs were subtracted from the raw food SPTs prior to analysis. If the newly derived SPT was negative, it was set to zero. Any SPT that was collected after the food challenge or collected more than 12 months before the

TABLE 2 | Baseline demographics.

Characteristic*	Total (n = 410)
Age in years, median (range)	9 (1–52)
Male	250 (61%)
Non-hispanic	390 (97%)
RACE	
Caucasian	250 (62%)
Black	6 (1%)
Asian	106 (26%)
Multiracial	37 (9%)
Other	5 (1%)
ATOPIC HISTORY	
Asthma	232 (62%)
Allergic rhinitis	284 (77%)
Atopic dermatitis	272 (74%)
Number of food allergens, median (range)	5 (1–16)
Mono-food allergic	8 (2%)
Total IgE (IU/L), median (range)	498.5 (18–3366)

**Count and percent of total subjects unless otherwise noted.*

challenge was excluded. If a subject had more than one value for either SPT or sIgE, then the value obtained most recently was used.

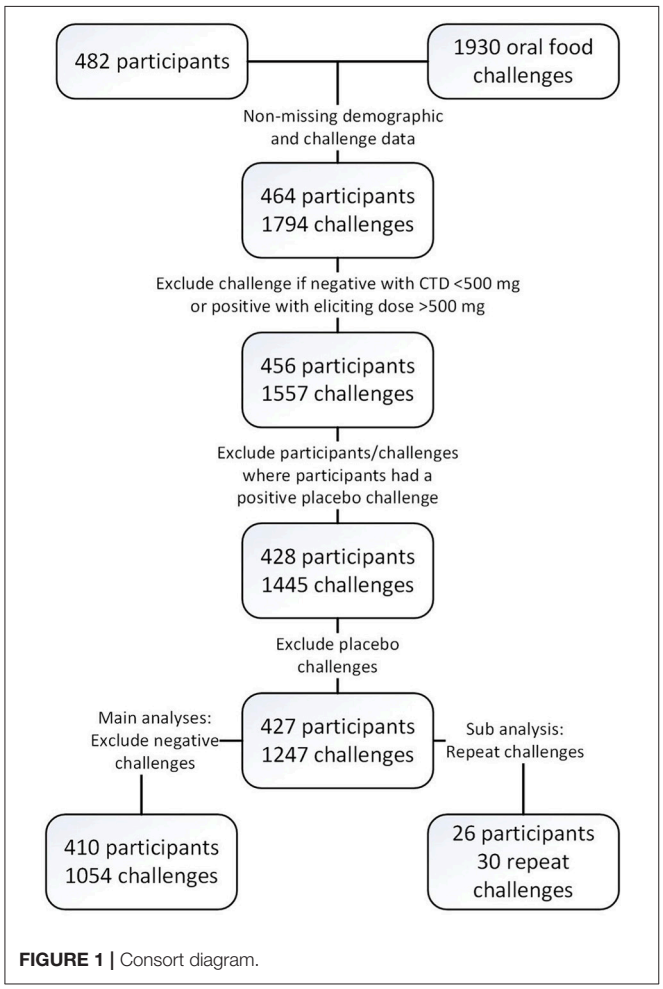

FIGURE 1 | Consort diagram.

In an effort to standardize OFCs across studies, challenges that were considered positive in their original studies based on thresholds higher than 500 mg but had cumulative tolerated doses (CTDs) of 500 mg or higher were re-classified as having negative challenges with no eliciting dose (ED) to a cumulative of 500 mg of protein. Subjects who had unknown or non-reported ethnicity were coded as missing ethnicity. Subjects with race of Native Hawaiian, other, or not reported were coded as other. Only positive challenge data were analyzed.

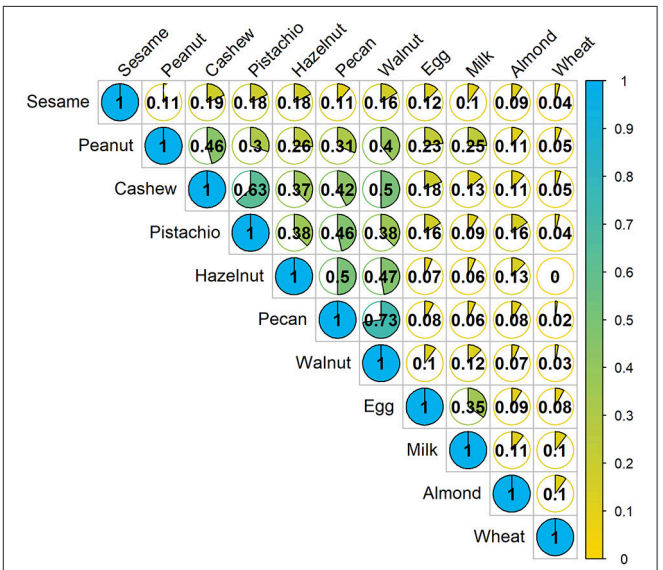

FIGURE 2 | Concurrent occurrences of food allergy based on food challenge outcomes: The fraction in each cell represents the Jaccard similarity coefficient, which is the amount of co-allergy accounting for the number of positive challenges for each allergen separately. Higher values indicate more similarity between the two allergens. Denominator only includes participants who were screened for multi-food allergy studies.

TABLE 3 | Eliciting dose (ED) thresholds by food.

Challenge Food	N	Number of subjects (% of total)	Eliciting dose (mg) median (range)	Eliciting dose curves (ED) (mg) (95% CI)		
				ED_5	ED_{10}	ED_{50}
Almond✠	30	29 (7)	25.0 (5–500)	0.86 (0, 1.92)	1.73 (0, 3.60)	20.77 (5.76, 35.78)
Cashew	151	150 (35)	25.0 (0.1–500)	0.07 (0, 0.13)	0.25 (0.05, 0.46)	8.78 (5.40, 12.16)
Egg	63	60 (14)	8.1 (0.1–500)	0.04 (0, 0.12)	0.18 (0, 0.42)	7.07 (2.61, 11.54)
Hazelnut	68	65 (15)	25.0 (1.6–500)	0.07 (0, 0.17)	0.29 (0, 0.68)	14.38 (5.36, 23.39)
Milk	67	66 (15)	32.7 (1.7–500)	0.21 (0, 0.49)	0.74 (0, 1.55)	20.41 (9.73, 31.09)
Peanut	347	330 (77)	75.0 (0.1–500)	0.49 (0.24, 0.73)	1.52 (0.89, 2.15)	29.90 (23.81, 35.98)
Pecan✠	88	88 (21)	25.0 (1.7–500)	0.38 (0.04, 0.71)	0.79 (0.19, 1.39)	10.68 (5.71, 15.64)
Pistachio	60	59 (14)	5.0 (5–275)	0 (0, 0.1)	0.01 (0, 0.04)	1.71 (0, 3.61)
Sesame	30	30 (7)	25.0 (5–500)	0.26 (0, 0.75)	0.88 (0, 2.24)	21.19 (5.28, 37.10)
Walnut	121	120 (28)	25.0 (1.7–500)	0.15 (0, 0.31)	0.56 (0.07, 1.05)	18.01 (10.54, 25.47)
Wheat	13	13 (3)	32.7 (5–500)	0.03 (0, 0.17)	0.16 (0, 0.75)	12.64 (0, 33.20)

All models fit to Weibull distribution unless otherwise noted by✠ (Log-normal).

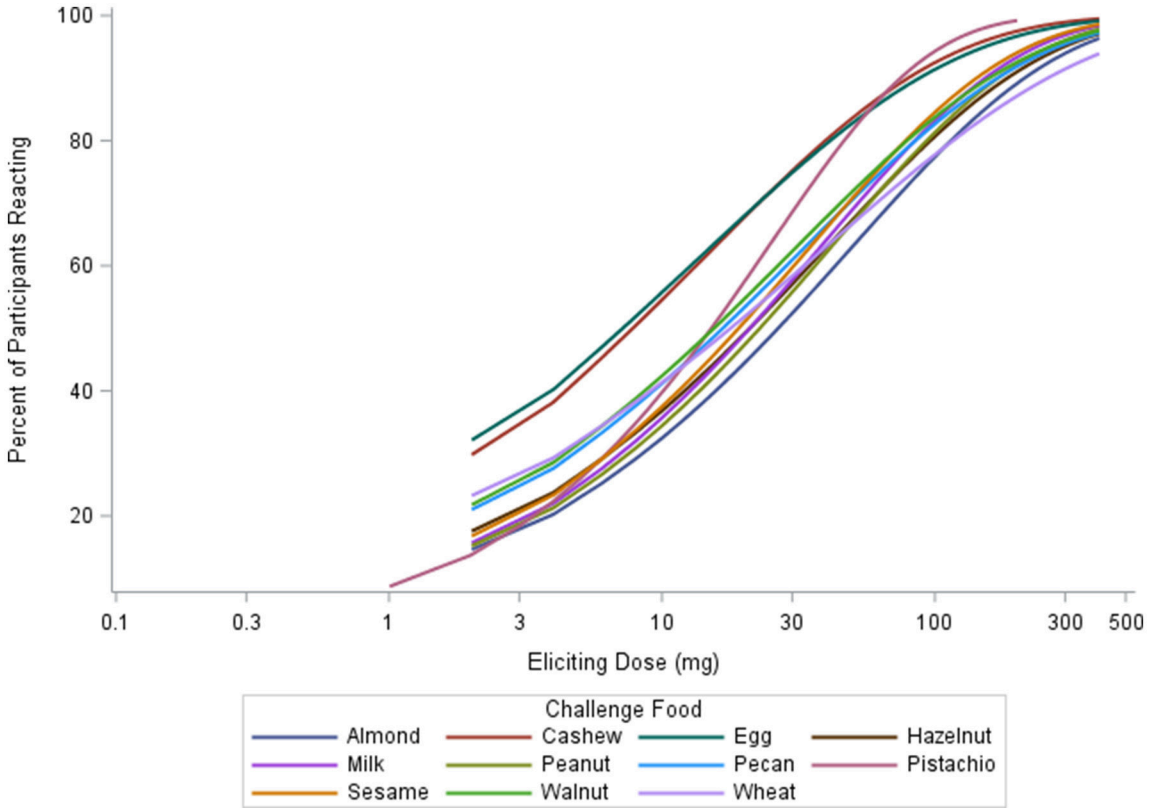

FIGURE 3 | Eliciting dose (ED) thresholds by allergen.

Statistical Analysis

To determine how often participants were allergic to multiple foods, pairwise comparisons of all major foods were conducted. The Jaccard similarity coefficient was implemented, accounting for the different number of participants allergic to each food (21). A detailed description of this method and its implementation in food studies has been previously published (22). Only participants who conducted food challenges for multi-food studies were included in this analysis.

To determine ED curves for each challenge food, data were analyzed using interval-censoring survival analysis fitted to three different probability distributions (Log-Normal, Log-Logistic, and Weibull) to estimate the ED for 5, 10, and 50% of patients (23).The three distributions were compared for each food, and the one with the lowest Akaike information criteria (AIC) was chosen. Interval-censoring analysis uses the lowest- and no-observed adverse effect levels (LOAELs and NOAELs) based on challenge information (23). If a participant reacted at the first challenge dose, the NOAEL was set to zero and the LOAEL was set to the first challenge dose. Turnbill intervals were implemented due to overlapping dose steps from various studies. The estimated ED and 95% confidence intervals were reported at each ED level. SAS's PROC LIFEREG was used to implement the analysis (24).

Multiple symptoms could have been reported during each challenge based on participant symptoms. Based on clinical reasoning, all 45 possible symptoms (3 grades for each of the 15 symptoms) were ranked in order of severity (**Table 1**). This list was then used to select the most "severe" symptom reported from each challenge. Therefore, only the most severe symptom reported [grade and SOC (system organ class)] was analyzed per challenge. Frailty models were fit to "time" (i.e., eliciting dose)

TABLE 4 | Adverse events by allergen and organ system.

	Number of AEs (% Total)				Total
Allergen	**Gastrointestinal**	**Respiratory**	**Skin**	**Other**	
Almond	9 (20.5)	3 (6.8)	32 (72.7)	0 (0.0)	44
Cashew	116 (37.2)	40 (12.8)	150 (48.1)	6 (1.9)	312
Egg	42 (36.8)	14 (12.3)	57 (50.0)	1 (0.9)	114
Hazelnut	22 (23.2)	10 (10.5)	63 (66.3)	0 (0.0)	95
Milk	23 (21.1)	14 (12.8)	71 (65.1)	1 (0.9)	109
Peanut	292 (36.7)	108 (13.6)	389 (48.9)	6 (0.8)	795
Pecan	49 (29.7)	20 (12.1)	95 (57.6)	1 (0.6)	165
Pistachio	26 (28.0)	6 (6.5)	61 (65.6)	0 (0.0)	93
Sesame	18 (39.1)	3 (6.5)	25 (54.3)	0 (0.0)	46
Walnut	61 (31.3)	23 (11.8)	110 (56.4)	1 (0.5)	195
Wheat	1 (7.1)	2 (14.3)	10 (71.4)	1 (7.1)	14
Total	666 (33.1)	247 (12.3)	1084 (53.8)	17 (0.8)	2014

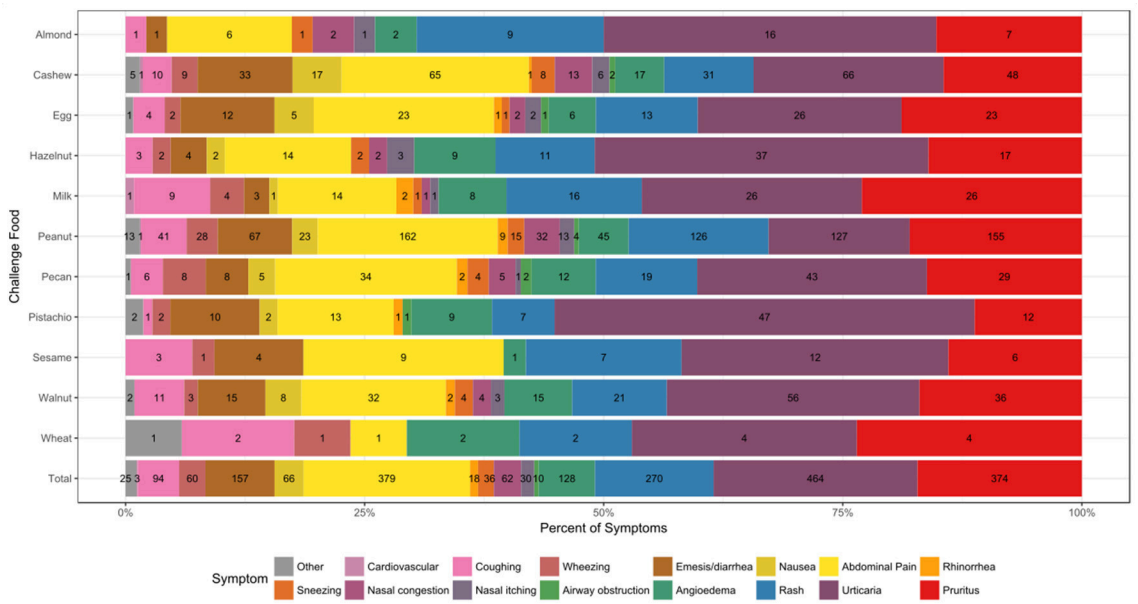

FIGURE 4 | Symptom type by allergen. Reaction counts are reported within the figure.

until the most severe symptom as a function of each clinical and demographic feature. An event was defined by whether or not the most severe symptom observed was a Bock grade 3. For each model, each participant contributed multiple observations corresponding to the number of food challenges. Due to possible correlations within participant or within food, random effects for participant and food were included in each model. Hazard ratios and 95% CIs were reported. Further, the correlation between ED and the severity ranking was measured by challenge food using the Spearman rank correlation test.

A subset of participants was challenged to the same food twice. The Kruskal-Wallis rank sum test was used to test whether ED changed from the first to second challenge. Spearman's rank order correlation was used to assess the association between change in ED and number of months between repeat challenges. These two tests were also used to assess changes in the symptom severity ranking. Lastly, Spearman's rank order correlation was also used to determine if change in ED was associated with change in symptom rank. *P*-values were reported.

All analyses were conducted at the 0.05 alpha level. No adjustments for multiple comparisons were made. Analyses were conducted using R v.3.4.3 (25) and SAS Software (24). Data are available and can be found on a secure REDcap database that is part 11 compliant.

RESULTS

Baseline Demographics

Age of participants ($n = 410$) ranged from 1 to 52, with a median age of 9 years old, and the cohort was comprised of mostly non-Hispanic (97%), Caucasian (62%), and males (61%). The majority of participants also had an atopic history, including asthma (62%), allergic rhinitis (77%), and atopic dermatitis (74%). The average number of doctor-diagnosed food allergies was 5, with only 2% of the cohort being mono-food allergic. The median total IgE (tIgE) was 499 kU/L (**Table 2**).

Challenge Overview

Four hundred and twenty-seven participants across multiple studies contributed 1,445 baseline challenges to the database (**Figure 1** and **Table 3**) of which 410 had 1,054 positive challenge outcomes. The most common positive challenge was for peanut ($n = 347$) followed by cashew ($n = 151$) and walnut ($n = 121$; **Table 3**). Seventy-seven percent of participants had a peanut allergy.

A Jaccard analysis assessing the similarity of co-allergy among the foods which were challenged in our cohort is illustrated in **Figure 2**. A higher similarity index corresponds to a higher degree of overlap of results obtained between two foods. Overall, higher similarity was observed within peanut and tree nut allergies compared to milk, egg, wheat or sesame. Allergies to pecan and walnut were 73% similar, followed by cashew and pistachio, which were 63% similar.

Eliciting Dose

The median ED was <35 mg of food protein for all foods, except for peanut, with the highest median ED at 75 mg, and pistachio, having the lowest at 5 mg (**Table 3**). Participants undergoing peanut challenges had the highest ED_{50} dose (i.e., the dose which elicits a reaction in 50% of subjects in those that ultimately react) of all foods (29.9 mg), followed by sesame (21.2 mg) and almond (20.7 mg). Pistachio had the lowest dose to elicit a reaction in 50% of subjects at 1.7 mg, however, only the participants with a positive reaction to cashew were

challenged with pistachio. Participants challenged with egg had the second lowest ED_{50} dose (7.07 mg). Across each of the three ED thresholds, almond and peanut consistently had the highest dose values. A higher percentage of participants challenged with egg and cashew reacted at lower EDs compared to other foods (**Figure 3**). Participants undergoing pistachio challenges had the largest increase in reactions over EDs than any other food, while participants with wheat had the lowest increase in percentage of participants reacting.

Adverse Events

A total of 2014 adverse events occurred during the 1,054 positive challenges (**Table 4**). The majority of adverse events occurred during peanut challenges ($n = 795$) followed by cashew ($n = 312$), which were also the most frequent challenges conducted. Within each food, adverse events related to skin were the most prevalent (54%), followed by GI events (33%). More specifically, urticaria and pruritus were the most common skin reactions, while abdominal pain was the most common GI reaction (**Figure 4**). The distribution of symptom type was similar across foods.

Table 1 lists the ordered rank of the potential adverse events that could occur during each participant's challenge, with lower ranked adverse events corresponding to more concerning symptoms. For example, severe cardiac symptoms, with a severity grade of 3, was ranked as number 45, compared to pruritus, with a severity grade of grade 1, which was ranked as number 1. Among the lower ranked adverse events (based on modified Bock criteria) (18), 673 (74%) were graded as mild, 134 (15%) as moderate, and 98 (11%) as severe (data not shown).

Participants with a history of asthma were more than twice as likely to have their most severe AE be a Bock grade of 3 at any point in their challenge compared to those without a history of asthma (hazard ratio [HR]: 2.37, 95% confidence interval [CI]: 1.36, 4.13; **Table 5**). Higher values of sIgE and sIgEr were significantly associated with higher risk of experiencing a severe reaction [HR: 1.49 [1.19, 1.85] and 1.84 [1.30, 2.59], respectively]. Participants who were challenged with cashew, peanut, pecan, sesame, and walnut had a higher severity ranking that was significantly associated with higher ED and, as ED increased, so did the severity (**Figure 5**).

Repeat Challenges

Of the 1445 total challenges (positive and negative), 30 were repeated by 26 participants. Only one participant had two repeat challenges to the same allergen (peanut), while all others only repeated a challenge to the same food once. Out of the 1054 positive baseline challenges, 21 were repeats with positive challenge outcomes, corresponding to 18 participants. Sixteen repeat challenges were to peanut, two to egg, and one each to almond, milk, and walnut (**Figure 6**). One participant had a repeat negative challenge to peanut and another had a repeat negative challenge to almond. The delta change in severity ranking from first to second challenge was significantly different from zero ($p = 0.04$; Wilcoxon signed rank test).

TABLE 5 | Univariate associations of severity.

Characteristic	Not Severe	Severe	Hazard ratio (95% CI)	Challenges included
Female	40%	39%	0.96 (0.6, 1.53)	905
Hispanic	98%	99%	1.11 (0.14, 8.74)	887
Race (ref = Caucasian)				895
Black	1%	1%	0.93 (0.11, 7.88)	
Asian	29%	37%	1.56* (0.95, 2.59)	
Multiracial	11%	5%	0.62 (0.23, 1.69)	
ATOPIC HISTORY				
Asthma	60%	76%	2.37** (1.36, 4.13)	825
Allergic rhinitis	77%	82%	1.1 (0.59, 2.04)	812
Atopic dermatitis	77%	75%	1.05 (0.59, 1.86)	813
Age	8	8	0.99 (0.96, 1.03)	905
FEV_1	99	99	1 (0.98, 1.03)	494
FEV_1/FVC	0.85	0.86	4.23 (0.04, 457.57)	492
Mono-Allergic	2%	2%	0.51 (0.09, 3.02)	905
Number of diagnosed food allergies	6	5	1 (0.93, 1.09)	905
sIgE (log-scale)	17	43	1.49*** (1.19, 1.85)	575
tIgE (log-scale)	439	583	1.2 (0.81, 1.78)	385
sIgEr (log-scale)	0.04	0.06	1.84*** (1.3, 2.59)	385
SPT	12	13.5	1.04* (1, 1.08)	600

*Each column corresponds to a single frailty model. SPT, skin prick test; sIgE, allergen-specific Immunoglobulin E; sIgEr, ratio of sIgE to total IgE (tIgE). Values in the "Not Severe" and "Severe" columns are the percentages, means, and medians for each characteristic on the raw scale. Median values are presented for age and each biomarker. *$p < 0.10$; **$p < 0.05$; ***$p < 0.01$.*

Additionally, the median time between repeat challenges was 735 days (range 2–982). While there was no difference in ED from the first to second challenge ($p = 0.66$), the severity rank significantly increased in the second challenge, corresponding to more severe symptoms experienced ($p = 0.02$, **Figure 6A**). By contrast, there was no significant association between change in ED and change in severity rank from the first to second challenge ($p = 0.14$, **Figure 6B**). Change in either ED or severity rank was not associated with time between repeat challenges ($p = 0.94$ and $p = 0.56$, respectively, **Figure 6C**).

DISCUSSION

The diagnosis of food allergy is highly complex (20, 26). Currently, SPT and sIgE are commonly used; however, these tests have a high false-positive rate, particularly in children, and lack specificity. Individuals who have a positive test but who do not have an allergic reaction to the allergen on ingestion are said to be sensitized to the allergen. Research on more reliable tests for diagnosing allergy such as the Basophil Activation Test (BAT), CRD, sIgE, IgG4, and total IgE (27) is ongoing. Currently, the gold standard for confirming food allergy (rather than food sensitization) is the DBPCFC (20, 26). However,

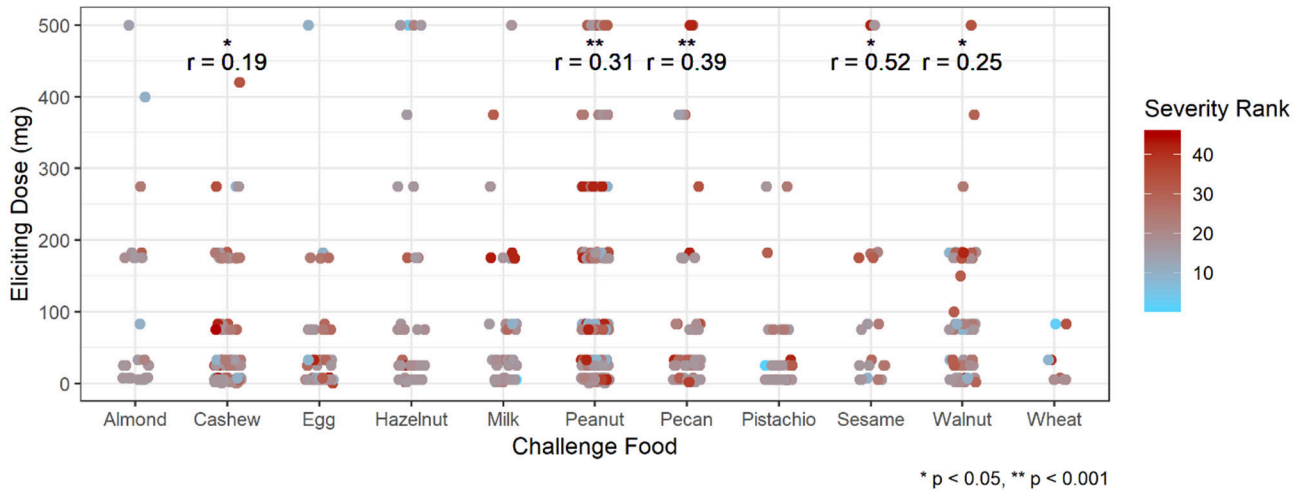

FIGURE 5 | Correlation of eliciting dose and adverse event severity ranking by challenge food. *$p < 0.05$, **$p < 0.001$ by Spearman rank correlation test. Red ranking corresponds to more severe symptoms, while blue corresponds to more mild symptoms.

there are several drawbacks in performing DBPCFCs. Presently, standardized dosing strategies for DBPCFCs are not widely practiced, and the optimal dosing schemes across allergens are unknown. DBPCFCs require multiple days of challenges which can significantly increase the cost. The most significant limitation is that food challenges carry the risk of potentially inducing severe anaphylaxis, which may require hospitalization or care in the intensive care unit (28), therefore DBPCFCs are typically performed under clinical supervision by trained staff who are able to recognize and treat any severe food reaction.

Our data show that the ED_{50} across all allergens is below 30 mg of protein; therefore safety in challenges may be increased by including additional steps at lower doses of the challenge. Compared to previously published thresholds by Blom et al. for cashew, egg, peanut, milk, and hazelnut (23), our findings of ED_5, ED_{10}, and ED_{50} were lower. One potential reason for this might be that the majority of our cohort was multi-food allergic (98%), and highly atopic with over 50% of the cohort with concurrent asthma, allergic rhinitis, and or atopic dermatitis. Additionally, the majority of our challenges had a dosing interval of 15 vs. 30 min reported by Blom et al. Participants undergoing peanut challenges had the highest ED_{50} dose (29.9 mg). Although pistachio had the lowest ED_{50} of 1.7 mg, it represented a small group of participants who had a previous reaction to a cashew challenge. The challenge of such subjects therefore was initiated at a lower dose (of 1 mg) due to safety concerns. Few studies have evaluated prognostic indicators for predicting OFC outcomes (29) and this is an area of ongoing research. In this study we attempted to identify potential prognostic indicators that may be associated with outcomes during OFC to a variety of foods, which could aid in risk stratification for allergists who may be considering a challenge. Our data suggest that food challenges with peanut, sesame, cashew, egg and walnut were more likely to be associated with GI-related symptoms, whereas hazelnut and milk were more likely to be associated with hives. The severity of the reacting symptom is also of concern when conducting a food challenge. Similar to what we and others have shown, a concomitant history of asthma increases the risk of having a severe reaction (29, 30). Not surprisingly, elevated specific IgEs and specific to total IgE ratios were associated with more severe symptoms. However, a severe reaction is possible even at low sIgE values (31). Often, the DBPCFCs conducted for inclusion of clinical trials have more stringent stopping rules and it is felt that more severe symptoms are elicited because of a higher ingested cumulative protein dose. When we assessed the severity of symptoms across doses, we found that severe symptoms were indeed modestly correlated with increasing doses for particular allergens (cashew, peanut, pecan, sesame, and walnut challenges). Perhaps we did not see this for all allergens due to insufficient sample size for those allergens.

In our data set, we also had the unique opportunity to assess ED and the severity of adverse events across repeat food challenges in a small subset of participants. We found that individuals had similar eliciting doses on the first and second challenge, with increasing severity on repeat challenges but with no association with time between challenges, which is consistent with prior findings of repeat challenges (32, 33). However, these results should be interpreted with caution as it is based on a small sample size, limited to 40 repeat challenges, constituting <4% of the total challenges in this cohort. Additionally, the analysis was not adjusted for allergen. Larger cohorts are needed to validate these preliminary findings. CRD was not done and this is a weakness of the paper and will be done in the future.

As food challenges and oral immunotherapy become more popular in outpatient clinics, our findings could

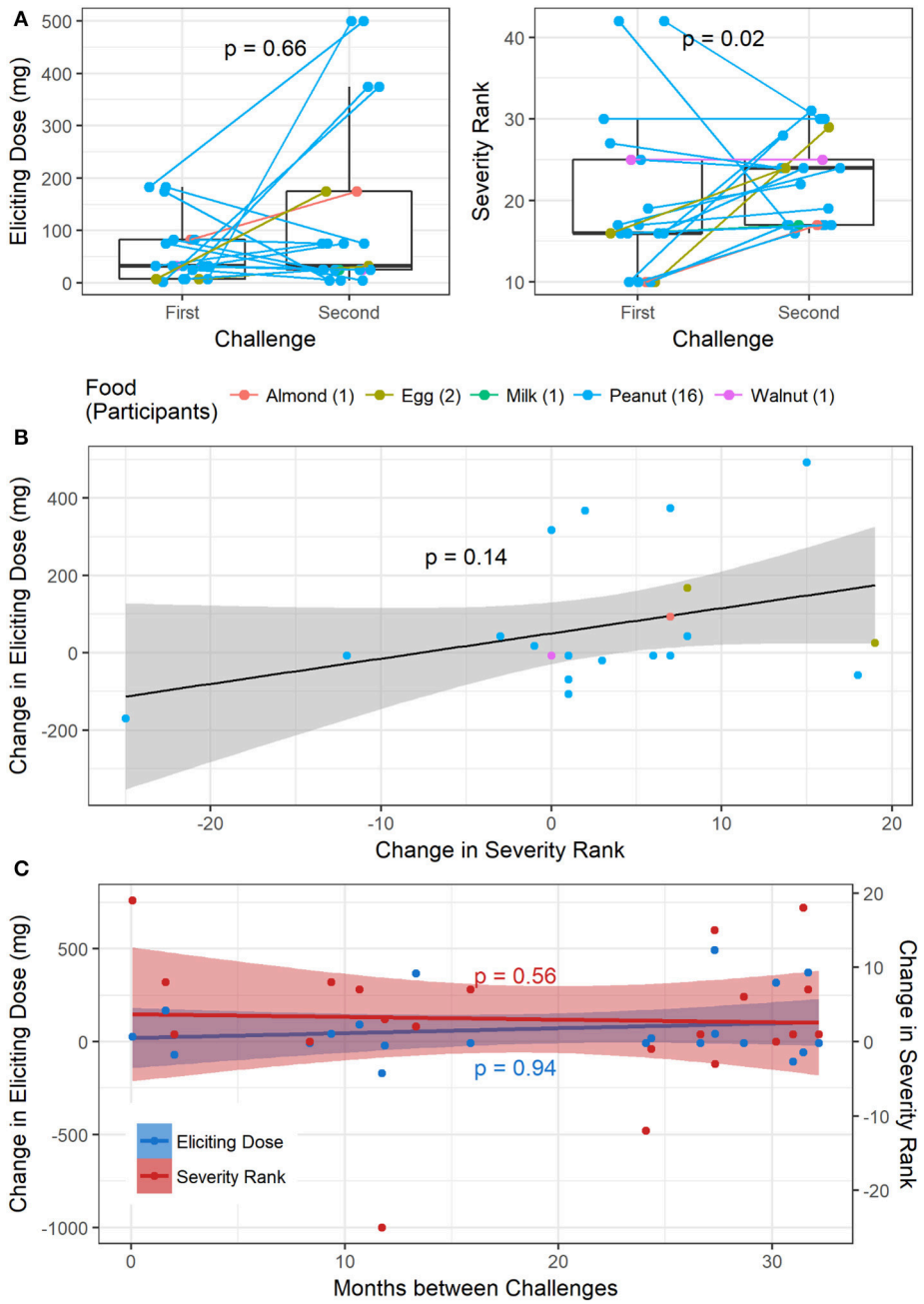

FIGURE 6 | Repeat challenges: **(A)** boxplot of change in ED and severity ranking from first to second challenge. **(B)** Association between change in ED and change in severity ranking. **(C)** Association between change in ED and time between challenges, and change in severity and time between challenges.

provide guidance and better insight into what to expect in performing food challenges in the outpatient clinic setting.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of ICH/GCP/CFR guidelines by the Stanford IRB with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Stanford IRB.

AUTHOR CONTRIBUTIONS

Study was designed by RC, AL, AS, SS, and KN. Study was conducted by RC, AL, AS, SS, AA, JP, JS, JT, ST, JW, and KN. Data analysis was conducted by NP, SA, MD, KN, KL, and MW.

Manuscript was written by RC, NP, SA, AL, AS, SS, SG, MD, and KN.

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