

Response to Docket No. FDA-2018-N-3809

Sesame as an Allergen in Foods

Submitted by:

*The Food Allergy Research & Resource Program of the University of Nebraska-Lincoln
Melanie Downs, Jamie Kabourek, Joe Baumert, Phil Johnson, and Steve Taylor*

The Food Allergen Labeling & Consumer Protection Act (FALCPA) requires the labeling of ingredients on packaged foods derived from eight food or food groups (milk, egg, fish, crustacean shellfish, peanut, soybean, tree nut and wheat). Ingredients derived from those foods must declare the source of the ingredient unless the ingredient has been exempted from source labeling. Sesame is not included among the eight foods or food groups that are subject to the source labeling provisions of FALCPA. On October 29, 2018, the Food & Drug Administration issued a request for information on the prevalence and severity of sesame allergy and on the prevalence of foods sold in the U.S. that are not currently required to declare the presence of sesame or an ingredient derived from sesame on the label.

The Food Allergy Research & Resource Program (FARRP) of the University of Nebraska – Lincoln wishes to respond to that request. We will provide comments on the prevalence, severity, and potency of sesame allergy. Additionally, FARRP has created and disseminated a survey to the food industry regarding the use of sesame and sesame-derived ingredients in foods and ingredients (spices, flavors, etc.) and labeling practices. FARRP will share the results of that survey with FDA as part of these comments.

Response Contents

The FDA request for information specified three topic areas for which scientific data and evidence were invited. This response addresses those three areas as follows:

- A. Prevalence of Allergies and Allergic Reactions Due to Sesame in the United States
 - Literature review
 - Pages 1-5
- B. Prevalence and Amounts of Undeclared Sesame in Foods
 - Results of food industry survey
 - Pages 5-12
- C. Possible Costs of Any Future Regulatory Action FDA Might Take Regarding Sesame
 - Results of food industry survey, continued
 - Pages 12-16

A. Prevalence of Allergies and Allergic Reactions Due to Sesame in the United States

Historical Development of Allergen Lists:

Based on the recommendations of an expert panel assembled in 1995 by FAO (the Food & Agriculture Organization), the Codex Alimentarius Commission identified eight foods/food groups that were recommended for clear and consistent labeling on packaged foods in 1999. The Codex list is identical to the list contained in FALCPA except that the U.S. list has wheat as opposed to cereals sources of gluten

in the Codex list. But the Codex list was based on concerns of food allergies and sensitivities including celiac disease while the list promulgated in FALCPA was focused only on food allergies (IgE-mediated food allergies). A current co-director of FARRP (SLT) was a member of that 1995 FAO Expert Panel. He notes that the panel recognized that the decision to put specific foods/food groups on the Codex list should have been based on the prevalence of allergies to those foods in the general population. However, in 1995, no clinical or scientific information existed on the population prevalence of specific food allergies. Thus the recommendations of the 1995 FAO Expert Panel were based heavily on the comparative prevalence of various food allergies among selected groups primarily food allergies among pediatric patients from allergy clinics in referral allergy centers. Very limited information was available in 1995 on the adult segment of the population. However, the Codex list has subsequently attained considerable notoriety including its apparent impact on the U.S. Congress as they developed FALCPA.

Subsequent to the adoption of the Codex list, public health authorities in various countries/regions developed their own allergen list. The criteria considered during the adoption of these allergen lists are not entirely clear in most cases but the lists do not appear to be based on clinical and scientific evidence. Sesame appears on the allergen lists of the European Union, Canada, and Australia/New Zealand among others. However, we strongly urge FDA to consider the addition to the U.S. food allergen list solely based on whether sufficient scientific and clinical evidence is available to justify the decision.

In their 2016 report, the National Academy of Medicine recommended “that the Center for Disease Control and Prevention obtain prevalence estimates on food allergy in a systematic and statistically sound manner.” [1] We strongly urge the adoption of that recommendation.

Criteria for Identifying Foods for Allergen Lists:

The International Life Sciences Institute-Europe (ILSI-EU) has assembled a series of panels to make recommendations about the criteria that should be used to identify those novel foods with the potential to become allergens of public health significance [2-4]. The main criteria are prevalence, severity, and potency. We urge FDA to use these same criteria to decide if sesame should be added to the allergen list in the U.S.

Prevalence of Sesame Allergy in North America:

The expert panel of the National Academy of Medicine noted in 2016 that accurate determination of the prevalence of food allergies and allergies to specific foods was challenging. Several factors can affect prevalence estimates including definition of the clinical condition, diagnostic criteria, the nature of the food challenge material, selection bias, non-participant bias, the timing of the survey, geographic region, and statistical issues. With sesame, the main concern is IgE-mediated, immediate hypersensitivity reactions. The simplest way to estimate prevalence involves use of a consumer or patient survey. However, patient surveys almost always over-estimate prevalence. Thus, studies that involve diagnostic criteria such as measurements of serum specific IgE levels and skin prick tests are stronger indicators of the true prevalence of a particular food allergy. However, serum specific IgE levels and skin prick tests assess sensitization to the food but do not prove that allergic reactions occur to that food. The gold standard to document reactivity to the food is a clinical oral challenge test, ideally a double-blind, placebo-controlled food challenge (DBPCFC). The most precise estimate of the prevalence of sesame allergy would involve the entire approach: survey, serum IgE measurement, skin prick test and food challenge. This approach has been recommended by the National Academy of Medicine [1] but has not been implemented for sesame or any other food in the U.S. Clearly, implementation of this

recommendation is necessary to truly understand the advisability of adding sesame to the U.S. allergen list.

The prevalence of sesame allergy in the U.S. and Canada is not precisely known. The most comprehensive data come from telephone surveys [5-8]. Self-reporting about food allergies leads to over-estimations of prevalence. For example, in a study of European adults across various regions of Europe, three times more respondents reported sesame allergy than were found to actually be sensitized to sesame [9]. Likely, even fewer participants would have been documented to have sesame allergies if oral challenges had been conducted. In another study conducted on the Isle of Wight (U.K.), 11.8% of 798 6yo children (94 children) had self-reported adverse reactions to foods [10]. However, when 83 of these 94 children underwent skin prick testing, only 12 children (14.4% of those self-reporting) were sensitized to any food on that basis. Further, 19 of these children had open food challenges (to 21 foods) and 10 of these children had positive reactions (52.6%); 6 of these 10 children consented to DBPCFC and only 3 of 6 children (50%) had positive reactions on DBPCFC. If these percentages hold across the entire group of 798 children, then 0.45% of the group with self-reported food allergy would be predicted to be confirmed as food-allergic by DBPCFC. The authors of this study also considered the likelihood of food allergy among the individuals who did not consent to the open or blinded food challenges and concluded that 1.6% or 13 of these children had confirmed food allergy on the basis of a positive DBPCFC, an open food challenge or a suggestive history and positive skin test to the food in question [10]. Sesame allergies were evaluated in this study but only 5 children were sensitized to sesame and only one child reacted upon open challenge.

In 2010, a random, digit-dial survey of food allergies was conducted in the U.S. [5]. The response rate was 42% involving 5300 households and 13,534 individuals. With a response rate of 42%, a non-participant bias is likely leading to an over-estimate of sesame allergy. The estimated prevalence of sesame allergy from this telephone survey was 0.1% [5]. A total of 13 cases of sesame allergy were identified including 3 children and 10 adults. This same survey estimated the prevalence of peanut and tree nut allergies which were much more commonly encountered than sesame allergy.

In 2018, a telephone and web-based survey was conducted in the U.S. involving 38,408 children; parent-proxy surveys were used [7]. The prevalence of sesame allergy was 0.2% [7], lower than the estimated prevalence rates for any of the other foods on the current U.S. list. Molluscan shellfish which are also not on the U.S. allergen list had an estimated prevalence of 0.6%, three-fold higher than sesame [7]. A total of 77 sesame-allergic children were identified through this survey. Among the sesame-allergic respondents to this survey, 55.5% had a physician-diagnosed food allergy and 86.4% had multiple food allergies [7].

Because food consumption patterns and population demographics are largely similar, the results of similar surveys conducted in Canada should also be considered. In 2010, a random digit-dial telephone survey was conducted among 10,596 households across Canada [6]. The response rate was 34.6% with results obtained for 9,667 individuals. The perceived prevalence of sesame allergy in Canada was 0.1% [6, 11]. The perceived prevalence was based entirely on the self-report of respondents. A probable response rate was also determined based on either a reported physician diagnosis of the sesame allergy or a described convincing history of sesame allergy. For sesame, the probable response was 0.09% [6], only a very slight decrease from the perceived prevalence. A confirmed response rate was additionally determined based on a combination of convincing clinical history of sesame allergy, a positive oral sesame challenge or a very positive serum IgE levels or skin prick test wheal size. The numbers of confirmed respondents were low and the confirmed prevalence rate decreased to 0.03% [6].

Subsequently, a survey was conducted of Canadian population groups that were likely under-represented in the 2010 survey, namely new citizens, immigrants, and aboriginal individuals [8]. Among these populations, the prevalence of sesame allergy was estimated at between 0.1 and 0.2% [8].

Several estimates exist of the prevalence of sesame allergy in children in other countries [12-15]. While not as relevant to the U.S. situation, the prevalence estimates in these children are similar to the U.S. at 0.05 – 0.2%. Some countries such as Israel may consume larger quantities of sesame making the likelihood of sesame allergies higher there [12].

All four of the North American telephone surveys estimate that the prevalence of sesame allergy is between 0.1 and 0.2% of the overall population. However, surveys based on self-reports are likely to lead to over-estimates [1]. The study of European adults suggests that 1/3 or fewer of self-reports are likely to be confirmed diagnostically [9]. The Isle of Wight study indicated that only 1.6% of children with self-reported food allergies would be confirmed by DBPCFC [10]. While the number of children with sesame allergy in the Isle of Wight study was small, not all self-reported cases of sesame allergy were confirmed by blinded challenges [10]. However, the 2018 U.S. survey noted that 55.5% of consumers indicating sesame allergy reported having a physician diagnosis. In the 2010 Canadian survey, 90% of consumers reporting sesame allergy had either a physician diagnosis or a convincing clinical history of reactivity to sesame [6]. Thus, there is agreement that the overall estimate of the prevalence of sesame allergy of 0.1 – 0.2% is inflated but less agreement about this extent of the over-estimate. As noted earlier, a systematic and statistically sound prevalence study in the U.S. as recommended by the National Academy of Medicine [1] is needed to determine the true prevalence of sesame allergy. If sesame allergies can only be confirmed by DBPCFC at a rate of 1.6% as suggested by the Isle of Wight study [10], then the prevalence of sesame allergy in North America would decrease to 0.0016 – 0.0032%.

Sesame allergy is apparently less prevalent than allergies to any of the other foods on the current U.S. allergen list [7]. The prevalence of soy and wheat allergies (the two lowest on the U.S. allergen list) are 2.5 times higher than the estimated prevalence of sesame allergy. Because of the low prevalence of sesame allergy by comparison to the other foods on the U.S. allergen list and the consistently low estimates of the prevalence of sesame allergy in the U.S. and Canada, we do not believe that the addition of sesame allergy to the allergen list can be supported on the basis of the prevalence of sesame allergy.

Severity:

Sesame is known to cause severe anaphylactic reactions on an occasional basis. Cases of severe anaphylactic reactions to ingestion of sesame have been reported in Australia [16], Italy [17], China [18], Sweden [19], England [20, 21], and throughout Europe [22]. The European Anaphylaxis Registry reported 12 severe reactions to sesame among a total of 1565 cases (0.8%) reported to the registry between July 2007 and March 2015 [22]. However, we are only aware of one reported fatal reaction [20]. Additionally, several well publicized cases of fatal reactions have occurred as reported in popular news media.

Certainly, sesame has the potential to elicit severe anaphylactic reactions with the potential of fatal outcomes. However, the prevalence of sesame in provoking severe allergic reactions is considerably lower than peanuts, tree nuts, milk, and eggs. Many foods currently not on the U.S. allergen list are able

to provoke severe anaphylactic reactions on an occasional basis. Thus we would assert that a decision to add sesame to the U.S. allergen list should not be made on the basis of severity alone.

Potency:

Limited research has been done on the potency of sesame as an allergic food. The VITAL (Voluntary Incidental Trace Allergen Labeling) Scientific Expert Panel of the Allergen Bureau of Australia and New Zealand has established a recommended Reference Dose for sesame protein of 0.2 mg [23]. The Reference Dose is the dose of protein from the allergenic food that is predicted to elicit objective symptoms at the 95% lowest confidence interval of the ED05, the dose provoking reaction in 5% of the sesame-allergic population [23]. The individual threshold doses (NOAELs and LOAELs) of an expanded cohort of sesame-allergic individuals resulted in predicted ED05 doses of 1.2 to 4.0 mg of sesame protein dependent on the choice of parametric model used to assess the population dose-distribution [24]. The Reference Dose for sesame protein is in the same range as the Reference Doses for peanut, milk, and hazelnut, higher than the Reference Doses for egg and mustard, and lower than the Reference Doses for soy, lupine, wheat and shrimp [23].

The evidence available suggest that sesame (in the form of sesame seed, flour or paste) has similar potency to other allergenic foods.

Reactions in the Community Due to Undeclared Sesame:

No published cases are known involving consumers reacting to undeclared sesame among products sold in the U.S. Certainly anecdotal cases abound but many of them are associated with restaurant or other foodservice products rather the packaged foods.

Globally, few studies have been done on reactions occurring in the community among individuals with diagnosed food allergies including sesame allergy. In the Netherlands, a 1-year survey was conducted of 157 adults with physician-diagnosed food allergies [25]. These consumers reported 73 adverse reactions over the single year period. In 51 cases, food samples were available for analysis and relevant food allergens were detected in 19 of those samples. Sesame was involved in only 2 of these 19 cases. In one product, 2.6 ppm undeclared sesame was detected (a Kaiser role). In the other case, 1690 ppm sesame was detected (prepackaged nougat). We cannot know if labeling practices are similar in the U.S. and the Netherlands. Thus this study only shows that undeclared sesame can pose a risk to sesame-allergic consumers.

B. Prevalence and Amounts of Undeclared Sesame in Foods

To our knowledge there are not any reports in the literature about the prevalence of sesame use in the food industry, nor about current industry practices for labeling of sesame-derived ingredients. In order to obtain information about the levels of use and labeling practices for sesame, a survey of food manufacturers was conducted.

Survey Production and Distribution

Four faculty members and one staff member from the Food Allergy Research and Resource Program (FARRP) at the University of Nebraska-Lincoln wrote and reviewed the survey prior to distribution. The

survey was conducted using the Qualtrics software platform, with an anonymous link provided to participants for them to submit responses within a 15-day time period.

Response Rates and Respondent Attributes

The survey access link was distributed to potential participants via email. Circulation of the survey included FARRP member companies (99 food manufacturers), the American Spice Trade Association (ASTA, 198 companies), the American Bakers Association (ABA, 90 companies), and companies represented by the Food Allergen Committee of the Grocery Manufacturers Association (GMA, 7 companies). The response rate for FARRP members was at least 35%, with 35 of 99 companies providing responses. In the case of ASTA and ABA, at least 15 (7.6%) and 3 (3.3%) companies provided responses, respectively. For 6 of the responses, the company and/or association affiliation was unknown.

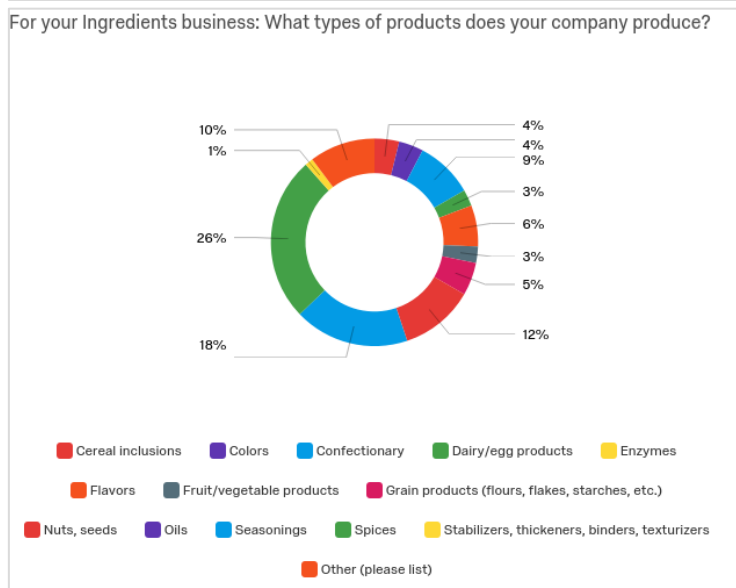
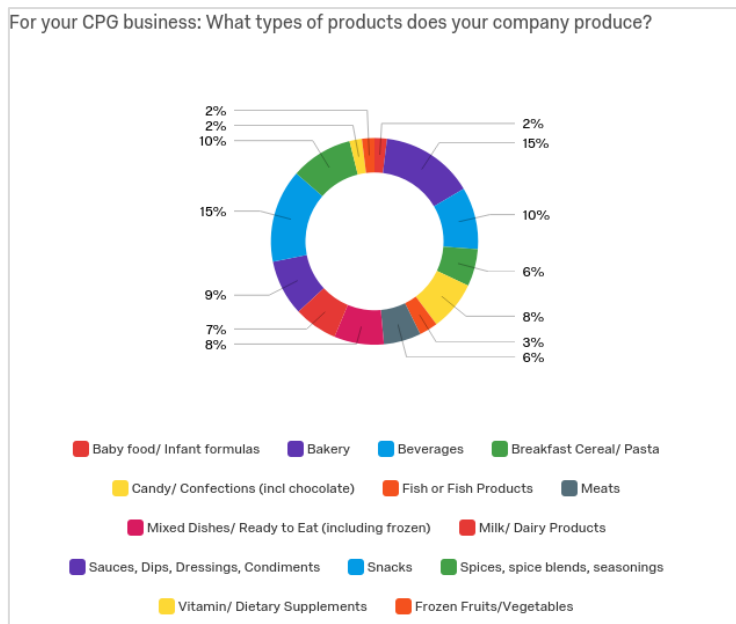


Figure 1: Respondent Product Categories

A total of 59 companies responded to the survey. Two additional responses had been submitted, but were duplicate responses from companies that had submitted another response and were therefore removed from the data analysis. The majority (35) of companies responding to the survey were large in size (>500 full-time employees; FTE), but 15 small (<100 FTE) and nine medium (100-500 FTE) companies also participated. The survey respondents represented manufacturers producing only consumer packaged goods (CPG, 34%), only ingredients (34%), and both CPG and ingredient products (32%). As CPG and ingredient manufacturers encounter different scenarios regarding the use and labeling of sesame, the questions asked of the participants were slightly different and the survey results will be presented separately in some cases.

The companies responding to the survey produce CPG products falling into a number of categories, as shown in **Figure 1**. The most frequently reported categories were bakery products (15%), snacks (15%), beverages (10%), and spices, spice blends, seasonings (10%). Many companies reported producing foods in

multiple categories. Ingredient manufacturers also indicated that they produced a variety of different products. Spices (26%), seasonings (18%), nuts and seeds (12%), and confectionary (19%) were among the most frequently reported categories of products.

Sesame Usage and Labeling

When CPG manufacturers were asked about whether any of their products contain sesame or any form of sesame-derived ingredients, 77% indicated that their company produced at least one sesame-containing product while 23% indicated that none of their company's products contained sesame. For ingredient manufacturers, 62% indicated they did produce sesame-containing products while 39% indicated they did not produce any sesame-containing products.

For those companies that did produce sesame-containing products, the most frequently-reported source of sesame was sesame seed (used by 44% and 50% of CPG and ingredient manufacturers, respectively), followed by highly-refined and cold/expeller pressed oils, as shown in **Figure 2**.

In order to assess both the prevalence of sesame usage and the presence of undeclared sesame, all survey respondents (including those that did not produce any sesame-containing products) were asked about the number of products that they produce. For CPG companies, it was recognized that some companies keep documentation based on stock-keeping units (SKUs), rather than based on product formulations, so respondents were able to provide data in numbers of products and/or numbers of SKUs. In some cases, a company may produce multiple SKUs from one product formulation, for example with different package sizes, different regional labels, etc. Some respondents gave information for both, while others only gave information for one measurement type. In addition, as all of the questions in the survey were voluntary, some participants only provided partial data. In such cases, ranges with and without partial data included are provided in **Table 1**.

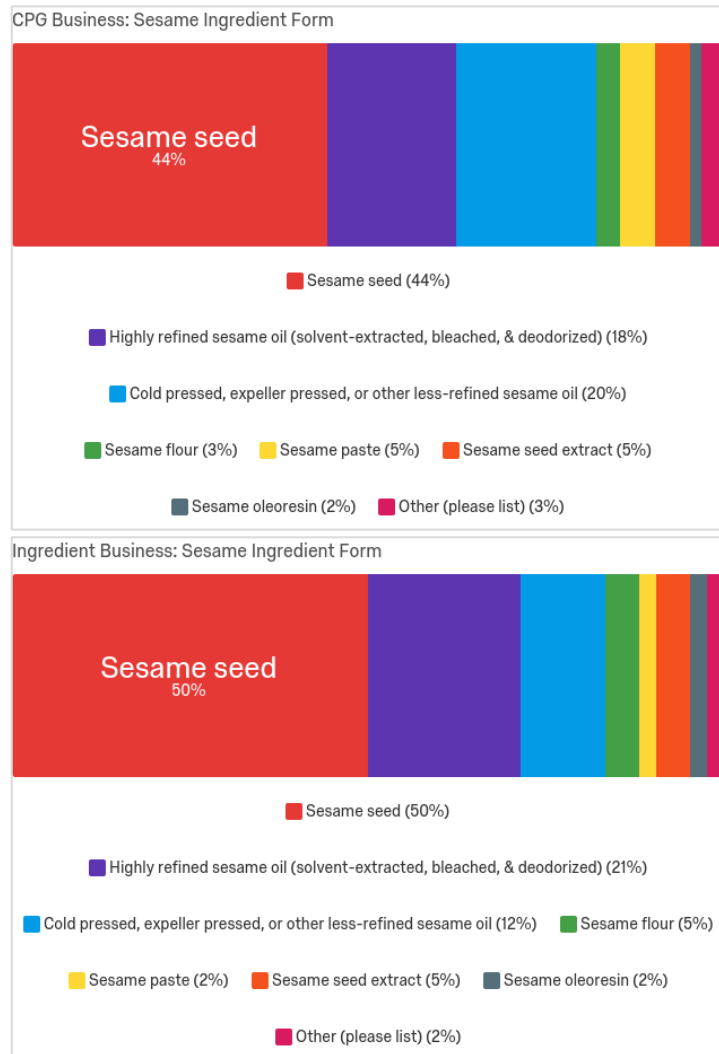


Figure 2: Sesame Ingredient Forms. Usage among manufacturers producing sesame-containing products

Table 1: Prevalence of Sesame Usage and Labeling

	<i>Number of Products</i>	<i>Percentage of All Products</i>	<i>Percentage of Sesame-containing Products</i>	<i>Number of SKUs</i>	<i>Percentage of All SKUs</i>	<i>Percentage of Sesame-containing SKUs</i>
CPG						
Total Number of Products Manufactured	38,013			106,362		
Products that Contain Sesame	563-631	1.5-1.7%		5,053-5,107	4.8%	
Products with Sesame Declared	553-562	1.5%	89.1-98.2%	5,035-5,036	4.7%	98.6%-99.6%
Products with Sesame Not Declared	10	0.03%	1.6-1.8%	18	0.02%	0.4%
Products with Sesame in Flavor	19	0.05%	3.0-3.4%	24	0.02%	0.5%
Products with Sesame in Spice	19	0.05%	3.0-3.5%	108	0.10%	2.1%
Products with Sesame in Incidental Additive	1	0.003%	0.2%	1	0.001%	0.02%
Products with Undeclared Sesame in Flavor	11	0.03%	1.7-2.0%	12	0.01%	0.2%
Products with Undeclared Sesame in Spice	4	0.01%	0.6-0.7%	6	0.01%	0.1%
Ingredients						
Total Number of Products Manufactured	42,249					
Products that Contain Sesame	1,139 -1,439	2.7-3.4%				
Products with Sesame Declared	939	2.2%	65%-82%			
Products with Sesame Not Declared	30 -330	0.07-0.78%	3%-23%			
Products with Sesame in Flavor	720	1.7%	50%			
Products with Sesame in Spice	286	0.7%	20%			
Products with Undeclared Sesame in Flavor	30		2.1%			
Products with Undeclared Sesame in Spice			0%			

CPG Manufacturers

In general, CPG manufacturers reported that sesame-containing products accounted for 1.5-1.7% of the total number products and 4.8% of the total number of SKUs manufactured. Of those products/SKUs that contained a sesame-derived ingredient, 89.1-99.6% included “sesame” in the ingredient statement. Ten products (18 SKUs) were reported as containing a sesame-derived ingredient that was not declared as “sesame” on the label (0.02-0.03% of all products and 0.4-1.8% of sesame-containing products).

CPG participants reporting that they produced sesame-containing products were also asked specifically about the presence of sesame in flavors, spice blends, colors, and incidental additives. Of those companies that produced sesame-containing products, 40% indicated sesame was present in a spice blend, 26% reported presence in a flavor, 5% (two respondents) reported presence in an incidental additive, and 29% reported that sesame was not present as part of any of these ingredients (**Figure 3**). No respondents indicated that sesame was part of a color. Of those participants that use spices that contain sesame-derived ingredients, 76% reported that they always declare sesame on the label. Of those companies that use flavors that contain sesame-derived ingredients, 45 and 27% indicated that they always or sometimes declare sesame, respectively.

Eleven CPG products were reported to contain an undeclared sesame-derived ingredient as part of a flavor and four as part of a spice. (No products were reported to contain undeclared sesame as part of a color or incidental additive.) In these cases, the flavors containing a sesame-derived ingredient were used at levels of 0.8-2.0%, and the spices containing a sesame-derived ingredient were used at levels of 0.1-0.4%. Products with undeclared sesame as part of a flavor or spice fell into five categories: snacks (8 products, 5 SKUs); sauces, dips, dressings, and condiments (5 SKUs); breakfast cereal/pasta (1 product, 1 SKU); other grain products (6 products, 6 SKUs); and plant protein products (1 SKU).

Ingredient Manufacturers

For ingredient manufacturers, 2.7-3.4% of products were reported as containing sesame, with sesame declared for the food industry customer in 65-82% of cases. Those participants reporting that undeclared sesame-derived ingredients are included in their products reported that a total of 330 ingredients contained undeclared sesame. However, 300 of those products were reported by a single survey participant, from which little additional information was available. So the main focus of this discussion will be on the remaining 30 products with reported undeclared sesame-derived ingredients. All of these 30 products were flavor ingredients. These flavors were reported to contain highly-refined (solvent-extracted, bleached, and deodorized) and/or less-refined (cold pressed, expeller pressed, etc.) sesame oils as the sesame-derived ingredients, both used at approximately 2% in the flavor formulations. One other respondent, while not indicating the number of products containing a sesame-derived ingredient, did indicate that sesame seed and sesame seed extract were used at levels 40% and 6.1%, respectively, in seasoning blend formulations with only sometimes declaring sesame for the food industry customer.

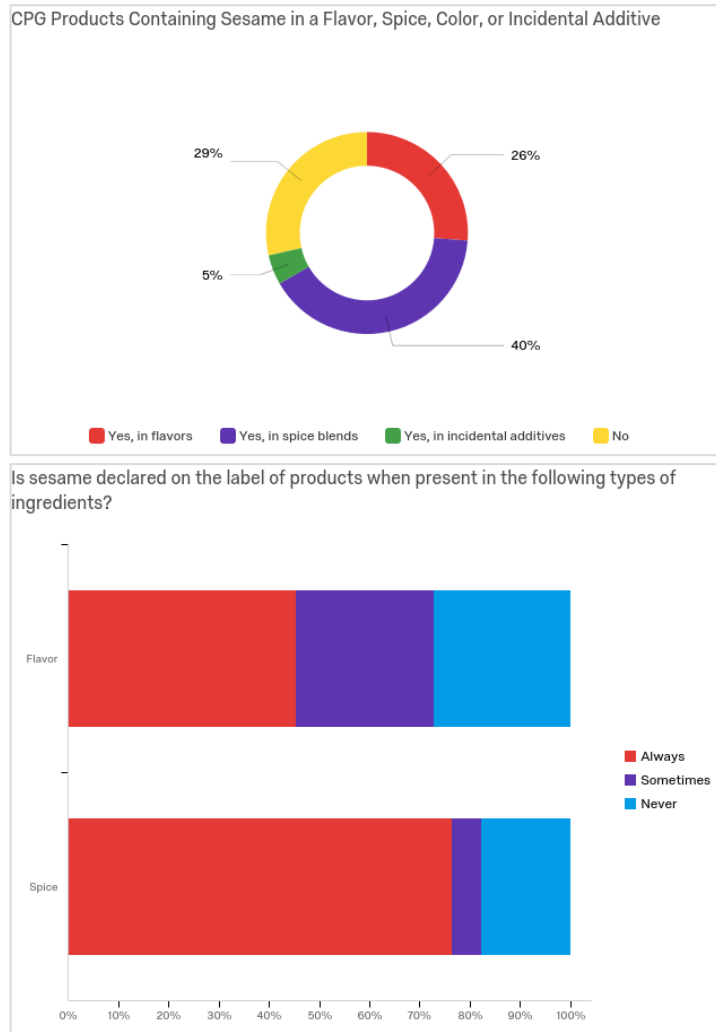


Figure 3: CPG Manufacturer Use and Labeling of Sesame in Flavors, Spices, Colors, and Incidental Additives.

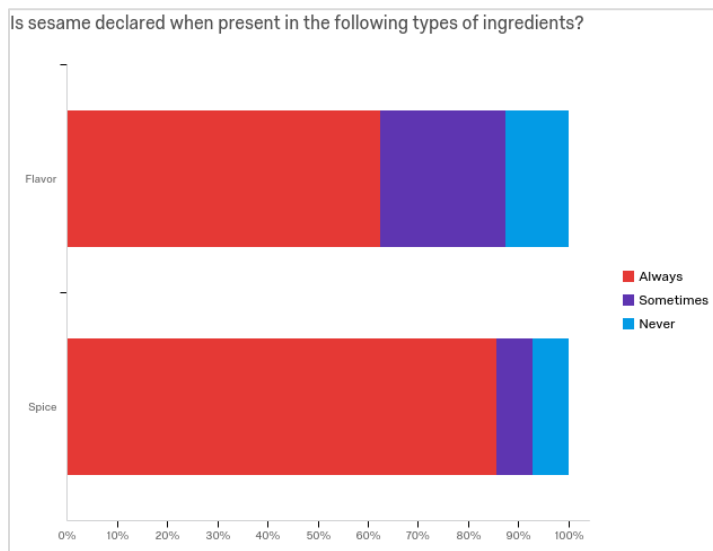
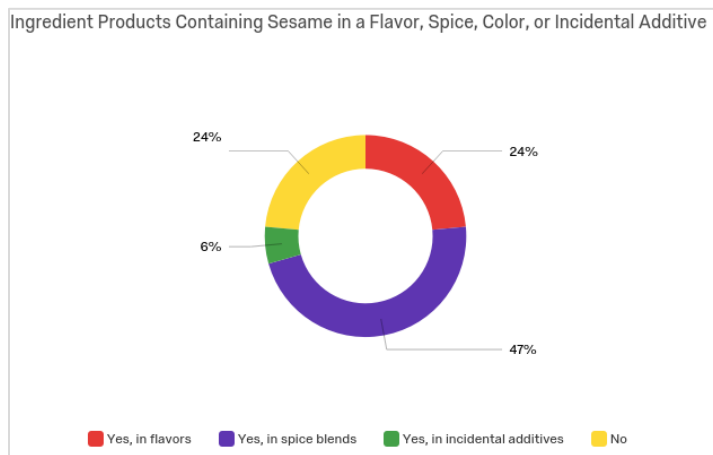


Figure 4: Ingredient Manufacturer Use and Labeling of Sesame in Flavors, Spices, Colors, and Incidental Additives.

Ingredient manufacturers were also asked in general about their production and use of sesame-containing ingredients. In the case of flavors, 21% indicated they produced flavors and 79% indicated they use flavors. For spices, 55% reported producing spice blends and 45% reported using spice blends. Ingredient manufacturers that did indicate the production of sesame-containing products reported similar rates of sesame-derived ingredients in flavors, spices, and incidental additives to those reported by CPG manufacturers, as shown in **Figure 4**. When present as part of a spice, 86% of ingredient manufacturers indicated that sesame was always declared, and when present in a flavor 63% indicated that sesame was always declared.

As discussed above, 30 products were indicated as containing undeclared sesame as part of a flavor ingredient. Additional comments from respondents indicated that whether sesame is declared when used in flavors may depend on the function of the sesame-derived ingredient, specifically sesame oils, which can be used to produce flavors or to serve as flavor carriers.

Estimated Sesame Protein Exposure from Flavors and Spice Blends

Based on the survey results, CPG manufacturers indicated that flavors and spices used in CPGs may contain an undeclared sesame ingredient. Ingredient manufacturers indicated that highly refined oils or less-refined oils (cold pressed, expeller pressed, etc.) were the sesame ingredients that were not always declared in flavors. Highly refined oils were exempted by Congress from the source allergen labeling requirements set forth by FALCPA, and therefore, highly refined sesame oil would not require source labeling if sesame were to be considered a priority allergen. Less-refined oils derived from priority allergenic sources do require source labeling. While less-refined oils do contain some residual protein, would less-refined sesame oil used as an ingredient in a flavor that is then used at a low percentage in a CPG constitute a risk to allergic sesame allergic individuals?

While no published studies were found that quantified the amount of residual sesame protein present in less-refined sesame oil, Rigby et al. [26] did evaluate the residual protein levels of highly refined and

partially/less refined soybean oils. Between 87-88 ppm soy protein (μg soy protein/g soy oil) was detected in less-refined oils. For the purposes of this exposure example, we conservatively assumed that less-refined sesame oil contains 100 ppm sesame protein.

Assuming that the flavors contain a maximum of 2% less-refined sesame oil (as reported by the ingredient manufactures) which contains 100 ppm sesame protein (0.01% sesame protein) and this flavor is used in the following food products at a maximum of 2% (as reported by CPG manufactures), a sesame-allergic individual would be exposed to the following mg doses of sesame protein if they consumed the reported FDA reference amount customarily consumed per eating occasion (RACC; 21CFR101.12) (Table 2).

Table 2: Estimated Sesame Protein Exposure from Flavors Containing Sesame Oil

Product Category	FDA RACC (g per Eating Occasion)	mg of Sesame Oil per RACC	mg of Sesame Protein per RACC	Fold-Lower than VITAL Reference Dose of 0.2 mg Sesame Protein
Sauces, Dips, Condiments	15	6	0.0006	333-fold lower
Snacks	30	12	0.0012	167-fold lower
Pasta (dry basis)	55	22	0.0022	91-fold lower
Breakfast Cereals	60	24	0.0024	83-fold lower

The VITAL (Voluntary Incidental Trace Allergen Labeling) Scientific Expert Panel of the Allergen Bureau of Australia and New Zealand has established a recommended Reference Dose for sesame protein of 0.2 mg [23]. Based upon the inclusion of less-refined sesame oil in flavors that are used in CPGs, a sesame-allergic individual would be exposed to ≤ 0.0024 mg of sesame protein in various products which is 83- or more fold lower than the 0.2 mg sesame protein Reference Dose of VITAL. To put this low level of exposure into a difference context, an exquisitely sensitive sesame-allergic individual with a threshold dose of 0.2 mg of sesame protein would need to consume approximately 5 kg of one of these food products during a single eating occasion in order to reach their 0.2 mg sesame protein threshold dose. Less-refined sesame oil used in a flavor that is not declared in a consumer packaged good would be unlikely to be a health hazard to sesame-allergic individuals. Other sesame derived ingredients such as sesame seeds, paste or flour which contain higher quantities of sesame protein could potential pose a risk to sesame-allergic individuals; however, these forms of sesame ingredients were nearly always reported by survey respondents to be declared on the product labels.

Sesame-derived ingredients may also be present in spice blends, but an insufficient number of complete survey responses were received to calculate estimated undeclared protein content values in finished products. The survey data can, however, provide an estimate of the frequency of usage of sesame-derived ingredients in this product category. Among ingredient suppliers, 23 indicated that they produce spices and/or seasonings (nine large, six medium, and eight small businesses). In aggregate, these companies produce a total of 17,224 products, 4.4% of which contain a sesame-derived ingredient. When sesame is used in a spice blend, 82% of the ingredient manufacturers indicated that sesame is always declared for their customers. Similarly 76% of CPG companies indicated that sesame is always declared on product labels when present in a spice blend.

Conclusions

In general, the results of the survey indicate that sesame is not widely used in the food industry (present in approximately 2% of products). In those products and ingredients that do contain sesame, sesame seed is the most commonly reported form of sesame-derived ingredient. When it is used, sesame is declared on the label of a large proportion of products (89-99% of CPG products). While 40% and 26% of CPG manufacturers reported the use of spice blends and favors, respectively, that contained a sesame-derived ingredient, 76% and 45% reported that sesame was always declared on the label when present in these ingredients. The presence of an undeclared sesame-derived ingredient was reported in **10 out of 38,031** total CPG products manufactured by the respondents. In most cases, when a sesame-derived ingredient was present but not declared on the label, it would result in very low levels of sesame protein due to a combination of the use of a low-protein ingredient (i.e. sesame oil) and/or low levels of usage of flavor ingredients.

The results of this survey may be subject to a few key limitations. First, the survey was primarily distributed to food manufacturers that are members of a program focused on food allergen research and management. As such, the survey respondents are likely to be more familiar with many aspects of food allergies, including sesame allergy, than other food manufacturers. These companies may also have more rigorous food allergen management practices in place. Second, the majority (59%) of survey respondents were large food manufacturers, and these companies are more likely to have resources available to dedicate towards knowledge and management of food allergens that not currently part of mandatory labeling regulations. Lastly, while all recipients of the survey were encouraged to participate, regardless of whether their company currently uses sesame, those companies that are currently manufacturing sesame-containing products may have had more interest in responding to the survey. Therefore, the prevalence of sesame usage could be over-estimated in the context of the entire food industry.

C. Possible Costs of Any Future Regulatory Action FDA Might Take Regarding Sesame

In addition to questions about their current use and labeling of sesame, survey participants were also asked about their current allergen control practices for sesame and the impact that adding sesame to the priority allergen list would have on their companies.

Current Allergen Control Practices for Sesame

CPG Manufacturers

Among CPG manufacturers, 38% reported managing sesame as part of an allergen control plan at both U.S. and international facilities, 15% reported only managing sesame as an allergen at international facilities, and 46% reported that they do not manage sesame as an allergen. Of those that do manage sesame as an allergen, 95% report that they inquire with their suppliers about the presence of sesame in their ingredients (71% for intentional presence and cross-contact, 24% for intentional presence only). Just over half of the respondents (52%) indicated that they currently conduct allergen change-overs for sesame.

When asked about current use of precautionary allergen labeling (PAL) for sesame, 79% of CPG companies indicated they do not use PAL for sesame and 21% of companies indicated that they do currently use PAL for sesame. Participants were also asked about how much they would expect the use of PAL to increase if sesame was added to the priority allergen list. Half of the respondents indicated they would expect to see some degree of increase in sesame PAL, with 15% reporting a great deal of increase in usage (Figure 5).

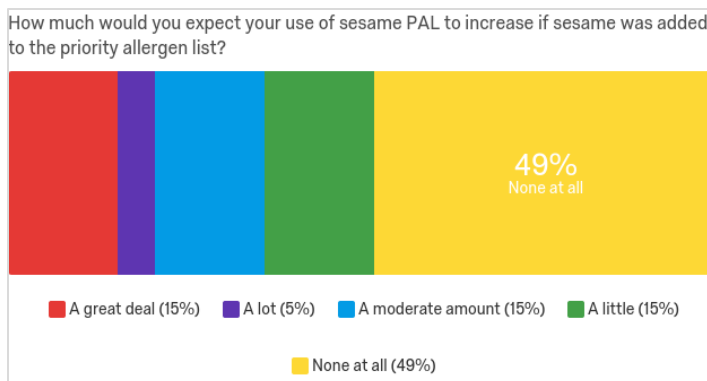


Figure 5: CPG Manufacturer Predicted Increase in Sesame PAL Usage

Ingredient Manufacturers

When asked about whether sesame was managed as an allergen as part of an allergen control plan, 54% of ingredient manufacturers indicated that it was in U.S. and international facilities, 3% reported it was only in international facilities, and 44% reported that it was not managed as an allergen. Within those companies that manage sesame as an allergen, 59% reported inquiring with suppliers about intentional presence and cross-contact with sesame, 32% inquiring for presence only, and 9% not inquiring with suppliers about sesame. In similar results to those seen for CPG manufacturers, 55% of ingredient manufacturers managing sesame as an allergen reported conducting allergen change-overs for sesame.

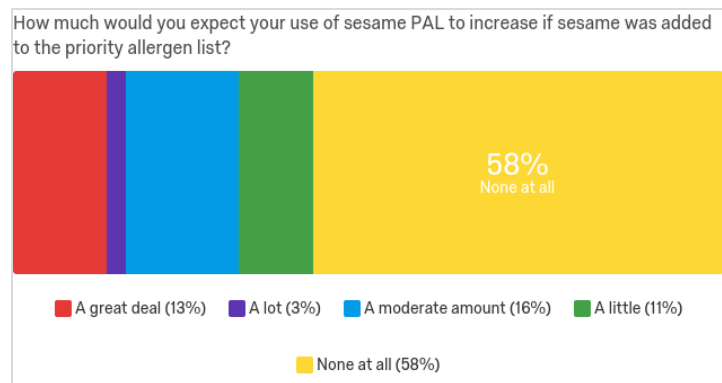


Figure 6: Ingredient Manufacturer Predicted Increase in Sesame PAL usage

On the topic of PAL for sesame, 90% of ingredient manufacturers indicated they did not use any form of PAL. If sesame were to be added to the priority allergen list, 42% of ingredient manufacturers would expect to see their use of PAL increase to some degree (Figure 6).

Impacts of Adding Sesame to the Priority Allergen List

In addition to questions about the prevalence and use of sesame in the food industry, the FDA Request for Information also included questions regarding the possible costs of future regulatory action. As we have noted in previously published studies, it is quite challenging to estimate the economic costs of food allergen management in the food industry [27]. Survey participants were therefore asked more generally about the magnitude of potential impacts if sesame were added to the priority allergen list. Several key aspects of allergen management were included in this assessment, including: changing labels and/or packaging, supplier verification activities, scheduling controls, allergen change-overs, and validation and testing.

CPG Manufacturers

The levels of impact reported by CPG manufacturers was found to be largely dependent on whether or not the company is currently producing products that contain sesame, as shown in **Figure 7**.

For those companies that are currently producing sesame-containing products, the areas in which the highest number of participants indicated that the addition of sesame would have a great deal or a lot of impact were validation and testing for sesame, allergen change-overs for sesame, and managing labels and/or packaging. For companies that do not produce any sesame-containing products, the primary area reported to likely have the largest impact was supplier verification activities.

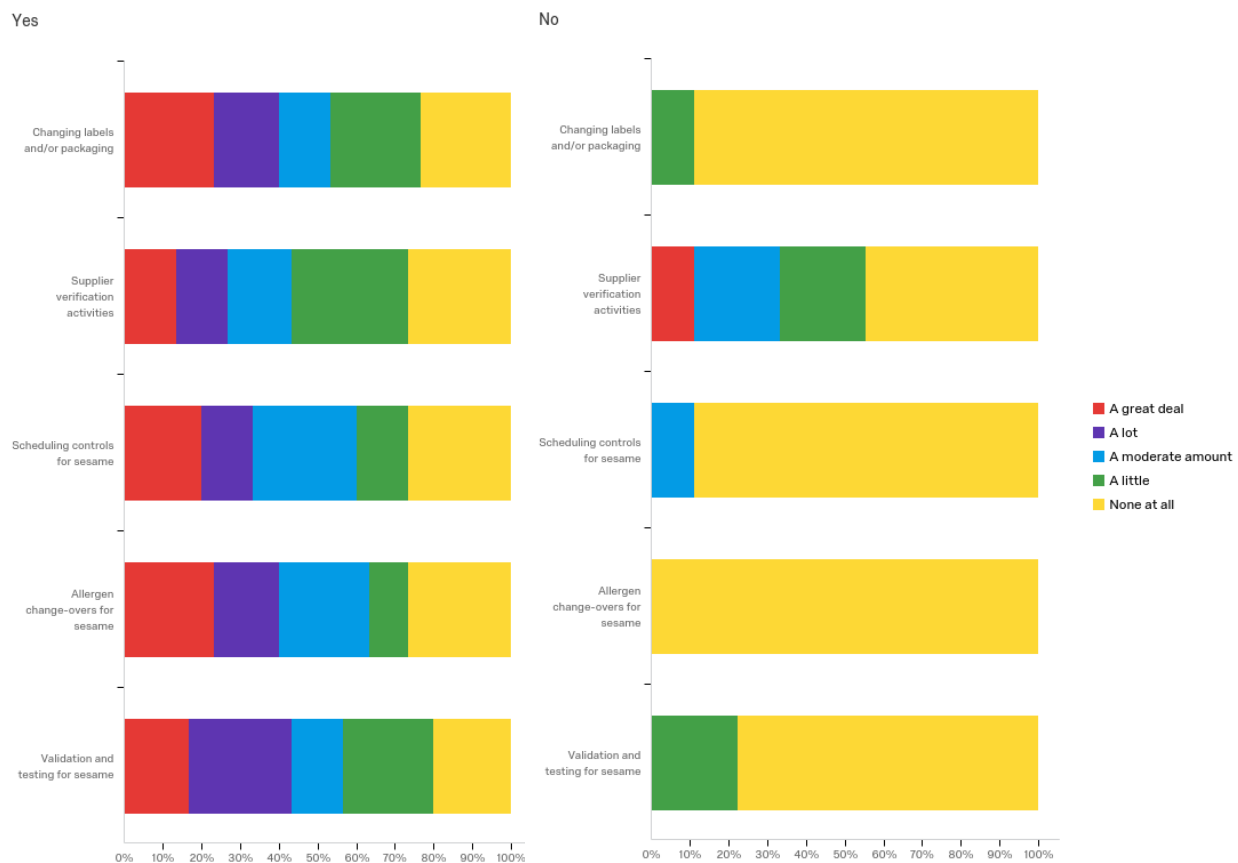


Figure 7: Impacts of Sesame as a Priority Allergen on CPG Manufacturers. Results are separated based on whether or not the company reported currently manufacturing products that contain sesame.

When asked more broadly about whether adding sesame to the priority allergen list would present other substantial challenges for the company, 26% responded that it would and 74% responded that it would not. In the qualitative comments provided by the participants who had indicated there would be substantial impacts, the time and resources required for sesame allergen change-overs was again frequently mentioned. For those that indicated adding sesame as a priority allergen would not have other substantial impacts on their company, many noted in the comments that they either do not currently produce sesame-containing products or they already handle sesame as an allergen due to international trade or harmonization of practices across multinational business units. It was also noted,

however, that even some manufacturers that currently always label for sesame would be required to change their product labels if they are currently using a Contains statement, as the Contains statement is required to be inclusive of all major allergens present in the product when it is used.

Ingredient Manufacturers

Similar to the results from the CPG manufacturers, ingredient manufacturers that are currently producing sesame-containing products most frequently reported that the allergen management areas that would be impacted a great deal or a lot by the addition of sesame to the priority allergen list were allergen change-overs for sesame and validation and testing for sesame (**Figure 8**). Also similar to the CPG results, those ingredient manufacturers not currently producing sesame-containing products would predict to experience the greatest impact with respect to supplier verification activities.

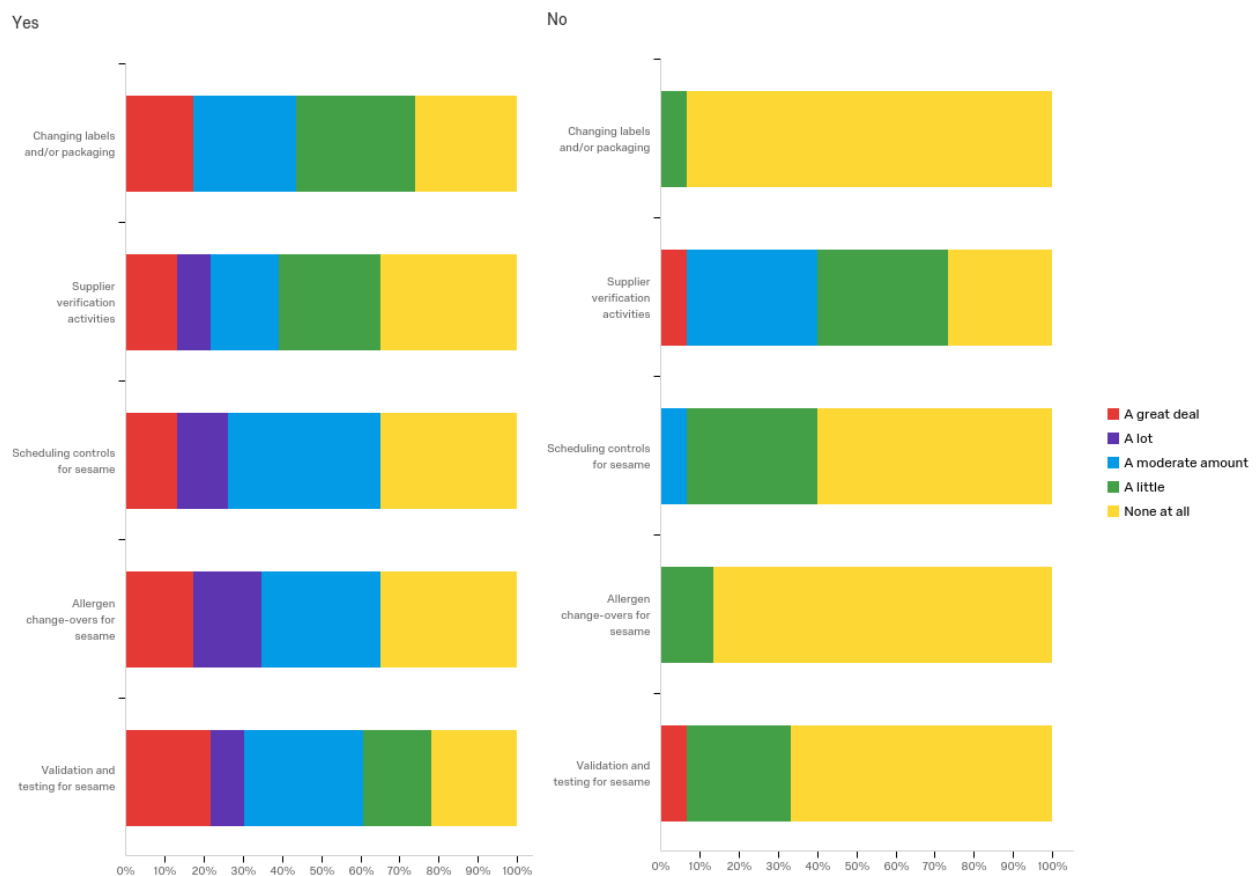


Figure 8: Impacts of Sesame as a Priority Allergen on Ingredient Manufacturers. Results are separated based on whether or not the company reported currently manufacturing products that contain sesame.

When asked about whether adding sesame as a priority allergen would have any other substantial impacts on their company, 18% of respondents answered yes and 82% answered no. Those participants that answered no frequently commented that they do not process sesame or that they already handle sesame as an allergen. Those participants indicating that there would be a substantial impact frequently commented about issues related to allergen change-overs and subsequent validation. Both of these results are similar to those from the CPG manufacturers.

Conclusions

These survey results indicate that including sesame as a priority allergen regulated in a similar fashion as the other current major allergens would have impacts beyond just changing product labels. Other aspects of allergen management such as cleaning and validation may present greater impacts and costs than the labeling of sesame itself. Sesame seeds, which were reported to be the most frequently used form of sesame-derived ingredient, pose a number of challenges with respect to equipment cleaning for allergen change-overs. Perhaps even more than other particulate allergens, validating that all sesame seeds have been removed from equipment is anticipated to be quite challenging for manufacturers due to the size and shape of these seeds. In addition, given that sesame seeds are commonly used in dry cleaning environments, such as bakeries, the ability of food manufacturers to completely remove sesame seeds may be limited. As noted by approximately 50% of respondents, these challenges may give rise to some degree of increase in PAL usage for sesame.

Based on the responses of the survey, the impacts and costs of adding sesame to the priority allergen list would be expected to be greater for some manufacturers than others. Those companies that currently process sesame-containing products but do not handle sesame as an allergen would be the most affected, and those impacts could be substantial. Companies that already treat sesame as an allergen in their U.S. facilities (38% and 54% of CPG and ingredient manufacturers) and/or do not produce sesame-containing products (23% and 39% of CPG and ingredient manufacturers) would be less impacted by any changes.

References

1. Committee on Food Allergies, *Finding a path to safety in food allergy assessment of the global burden, causes, prevention, management, and public policy*, V.A. Stallings and M.P. Oria, Editors. 2016: Washington DC. p. 579.
2. Björkstén, B., et al., *Criteria for identifying allergenic foods of public health importance*. Regulatory Toxicology and Pharmacology, 2008. **51**: p. 42-52.
3. van Bilsen, J.H.M., et al., *Evaluation of scientific criteria for identifying allergenic foods of public health importance*. Regulatory Toxicology and Pharmacology, 2011. **60**(3): p. 281-289.
4. Chung, Y.J., et al., *Application of scientific criteria to food allergens of public health importance*. Regulatory Toxicology and Pharmacology, 2012. **64**(2): p. 315-23.
5. Sicherer, S.H., et al., *US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up*. Journal of Allergy and Clinical Immunology, 2010. **125**: p. 1322-1326.
6. Ben-Shoshan, M., et al., *A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada*. Journal of Allergy and Clinical Immunology, 2010. **125**: p. 1327-1335.
7. Gupta, R.S., et al., *The Public Health Impact of Parent-Reported Childhood Food Allergies in the United States*. Pediatrics, 2018. **142**(6): p. e20181235.
8. Soller, L., et al., *Prevalence and Predictors of Food Allergy in Canada: A Focus on Vulnerable Populations*. The Journal of Allergy and Clinical Immunology: In Practice, 2015. **3**(1): p. 42-49.
9. Burney, P.G.J., et al., *The prevalence and distribution of food sensitization in European adults*. Allergy, 2014. **69**(3): p. 365-371.

10. Venter, C., et al., *Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study*. *Pediatric Allergy and Immunology*, 2006. **17**: p. 356-363.
11. Soller, L., et al., *Overall prevalence of self-reported food allergy in Canada*. *Journal of Allergy and Clinical Immunology*, 2012. **130**(4): p. 986-988.
12. Dalal, I., et al., *Food allergy is a matter of geography after all: sesame as a major cause of severe IgE-mediated food allergic reactions among infants and young children in Israel*. *Allergy*, 2002. **57**: p. 362-365.
13. du Toit, G., et al., *Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy*. *Journal of Allergy and Clinical Immunology*, 2008. **122**: p. 984-991.
14. Zuidmeer, L., et al., *The prevalence of plant food allergies: a systematic review*. *Journal of Allergy and Clinical Immunology*, 2008. **121**: p. 1210-1218.
15. Emmett, S.E., et al., *Perceived prevalence of peanut allergy in Great Britain and its association with other atopic conditions and with peanut allergy in other household members*. *Allergy*, 1999. **54**(4): p. 380-385.
16. de Silva, I.L., et al., *Paediatric anaphylaxis: a 5 year retrospective review*. *Allergy*, 2008. **63**: p. 1071-1076.
17. Asero, R., et al., *A case of sesame seed-induced anaphylaxis*. *Allergy*, 1999. **54**(5): p. 526-527.
18. Ji, K., et al., *Anaphylactic shock and lethal anaphylaxis caused by food consumption in China*. *Trends in Food Science & Technology*, 2009. **20**: p. 227-231.
19. Yman, I.M., *Detection of inadequate labelling and contamination as causes of allergic reactions to food*. *Acta Alimentaria*, 2004. **33**: p. 347-357.
20. Pumphrey, R.S.H. and M.H. Gowland, *Further fatal allergic reactions to food in the United Kingdom, 1999-2006*. *Journal of Allergy and Clinical Immunology*, 2007. **119**: p. 1018-1019.
21. Pumphrey, R.S.H. and S.J. Stanworth, *The clinical spectrum of anaphylaxis in north-west England*. *Clinical and Experimental Allergy*, 1996. **26**(12): p. 1364-1370.
22. Grabenhenrich, L.B., et al., *Anaphylaxis in children and adolescents: The European Anaphylaxis Registry*. *Journal of Allergy and Clinical Immunology*, 2016. **137**(4): p. 1128-1137.e1.
23. Taylor, S.L., et al., *Establishment of Reference Doses for Residues of Allergenic Foods: Report of the Vital Expert Panel*. *Food and Chemical Toxicology*, 2014. **63**: p. 9-17.
24. Dano, D., et al., *Sesame allergy threshold dose distribution*. *Food and Chemical Toxicology*, 2015. **83**: p. 48-53.
25. Blom, W.M., et al., *Accidental food allergy reactions: Products and undeclared ingredients*. *Journal of Allergy and Clinical Immunology*, 2018. **142**(3): p. 865-875.
26. Rigby, N.M., et al., *Quantification and partial characterization of the residual protein in fully and partially refined commercial soybean oils*. *Journal of Agricultural and Food Chemistry*, 2011. **59**: p. 1752-1759.
27. Gupta, R.S., et al., *Economic Factors Impacting Food Allergen Management: Perspectives from the Food Industry*. *Journal of Food Protection*, 2017. **80**(10): p. 1719-1725.