7-10-2023

Sesame eliciting and safe doses in a large sesame allergic population

Liat Nachshon

Joost Westerhout

W. Marty Blom

Benjamin Remington

Michael B. Levy

See next page for additional authors

Authors

Liat Nachshon, Joost Westerhout, W. Marty Blom, Benjamin Remington, Michael B. Levy, Michael R. Goldberg, Naama Epstein-Rigbi, Yitzhak Katz, and Arnon Elizur

Received: 11 April 2023 | Revised: 2 July 2023 | Accepted: 10 July 2023

DOI: 10.1111/all.15863

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Sesame eliciting and safe doses in a large sesame allergic population

Liat Nachshon[1,2] | Joost Westerhout[3] | W. Marty Blom[3] | Benjamin Remington[4] | Michael B. Levy[1] | Michael R. Goldberg[1,5] | Naama Epstein-Rigbi[1,5] | Yitzhak Katz[1,5] | Arnon Elizur[1,5]

[1]Institute of Allergy, Immunology and Pediatric Pulmonology, Yitzhak Shamir Medical Center, Be'er Ya'akov, Israel

[2]Department of Medicine, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[3]The Netherlands Organization for Applied Scientific Research TNO, Utrecht, The Netherlands

[4]Food Allergy Research and Resource Program, Department of Food Science and Technology, University of Nebraska, Lincoln, Nebraska, USA

[5]Department of Pediatrics, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Correspondence
Arnon Elizur, Institute of Allergy, Immunology and Pediatric Pulmonology, Building 131, Yitzhak Shamir Medical Center, Zerifin 70300, Beer Yaakov, Israel.
Email: elizura@gmail.com

Abstract

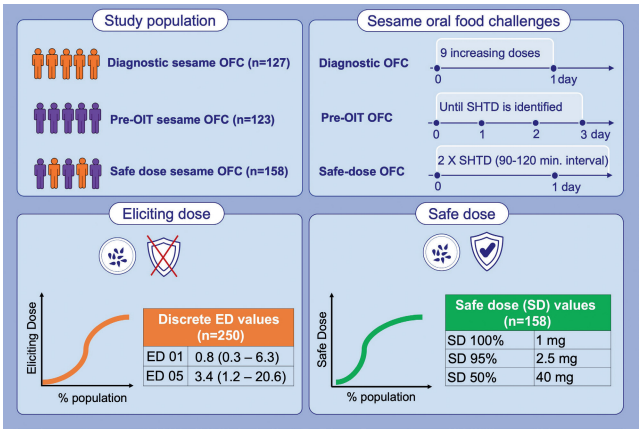
Background: Sesame is a significant food allergen causing severe and even fatal reactions. Given its increasing prevalence in western diet, sesame is listed as an allergenic food requiring labeling in the United States and EU. However, data on the population reaction doses to sesame are limited.

Methods: All sesame oral food challenges (OFCs), performed either for diagnosis or for threshold identification before the beginning of sesame oral immunotherapy (OIT) between November 2011 and July 2021 in Shamir medical center were analyzed for reaction threshold distribution. Safe-dose challenges with 90–120 min intervals were also analyzed.

Results: Two hundred and fifty patients underwent 338 positive OFCs, and additional 158 safe-dose OFCs were performed. The discrete and cumulative protein amounts estimated to elicit an objective reaction in 1% (ED01) of the entire cohort ($n = 250$) were 0.8 mg (range 0.3–6.3) and 0.7 mg (range 0.1–7.1), respectively, and those for 5% of the population (ED05) were 3.4 mg (range 1.2–20.6) and 4.5 mg (range 1.2–28.8), respectively. Safe-dose OFCs showed similar values of ED01 (0.8, 0.4–7.5 mg) and ED05 (3.4, 1.2–22.9 mg). While doses of ≤1 mg sesame protein elicited oral pruritus in 11.6% of the patients, no objective reaction was documented to this amount in any of the challenges, including safe-dose OFCs.

Conclusions: This study provides data on sesame reaction threshold distribution in the largest population of allergic patients studied, with no right or left censored data, and with validation using a safe-dose OFC. It further supports the current methods for ED determination as appropriate for establishing safety precautions for the food industry.

KEYWORDS
adverse reactions, eliciting dose, reaction threshold, safe dose, sesame allergy



GRAPHICAL ABSTRACT

Two hundred and fifty patients underwent sesame OFCs (diagnostic, $n = 127$; pre-OIT, $n = 123$). Safe-dose (based on identified SHTD) challenges with 90–120 min intervals were analyzed in a subgroup of 158 patients. The discrete ED01 and ED05 of the entire cohort were 0.8 mg and 3.4 mg, respectively, and estimated values of discrete ED01 and ED05 from safe-dose OFCs were similar. Importantly, no objective reaction was documented to a dose of ≤1 mg sesame protein.

1 | INTRODUCTION

Verifying food safety for individuals with food allergy is becoming a significant concern for the food industry, and labeling of allergenic foods is required by law in many countries.[1–3] The food industry often uses precautionary allergy labeling such as "may contain", for fear of allergic reactions to minimal amounts of protein.[4,5] However, this approach significantly restricts the variety of food products available for food allergic individuals. Risk-assessment approaches attempt to define doses which would elicit a reaction in 1% (ED01) and 5% (ED05) of the allergic population, with the assumption that the threshold for allergic reaction lies between a subjects' no observed adverse effect level (NOAEL) and his lowest observed adverse effect level (LOAEL).[6,7] ED01 and ED05 values were determined for the most common allergenic foods.[8,9] However, many of these studies are limited by small sample sizes or by inclusion of OFCs whose protocol does not enable NOAEL and LOAEL determination.[8,9] In addition, while most analyzed OFCs included dose increases with few minutes intervals, objective symptoms of an allergic reaction may appear after a longer interval (median 55, range 5–210 min).[10,11] Although prospective studies for determination of threshold levels with dose intervals of up to 120 min, were also conducted,[12,13] those were performed for only a few allergens. Eliciting doses have been determined for 14 priority food allergens,[8,9] but the level of information to substantiate these EDs is variable.[14]

Sesame is a significant food allergen, known to cause severe and even fatal allergic reactions, and which is becoming increasingly abundant in the Western diet.[15–17] Its labeling is required by the European Union (EU) and by other countries.[18] On April 23, 2021, the Food Allergy Safety, Treatment, Education, and Research (FASTER) Act was signed into law, declaring sesame as the 9th major food allergen recognized by the United States. As a result, starting January 1, 2023, labeling of sesame as an allergen is required in the United States.[19] To date, data on reaction thresholds to sesame is derived from small samples.[20–29] In addition, significant variability exists between published protocols of sesame OFCs. These include the use of different sesame products, some with unclear protein content,[21–23,27–29] inability to determine NOAEL due to reactions to the first (high) dose ("left censor" error),[20–24] inability to determine LOAEL, due to the use of subjective criteria to terminate OFCs ("right censor" error),[10,21] and the use of populations who are restricted in age and in food allergy severity.[20,24–28] None of the published sesame OFCs included sufficiently long intervals between doses to ensure accurate determination of a safe dose, and overall, reliable information regarding sesame eliciting dose is limited.[30] An analysis combining 246 OFCs from 11 different studies was recently published in attempt to overcome these limitations. The discrete ED01 and ED05 were 0.2 mg and 2.4 mg, respectively.[31] When excluding studies with significant left censors, the ED01 and ED05 in the remaining 172 patients were higher, 0.4 mg and 3.4 mg, respectively.[31]

The current study aims to provide information regarding reaction thresholds to sesame in the largest population studied thus far with no left or right censors, and to verify the results using a safe-dose challenge.

2 | METHODS

This is a retrospective study, based on analysis of information that was drawn from previous studies and clinical practice database. The protocols used for OFCs were a priori designed to enable the analysis of reaction thresholds.

2.1 | Patients

All patients who underwent a sesame OFC, either diagnostic (diagnostic-OFC), or for threshold identification before the beginning of sesame-OIT (OIT-OFC) between November 2011 and July 2021 in the Institute of Allergy, Immunology and Pediatric Pulmonology

at Shamir (formerly Assaf-Harofeh) medical center were included. Helsinki committee approval for review and publication of the data was obtained. Patients underwent a diagnostic-OFC if the history of allergic reaction to sesame was equivocal, or if they had no allergic reaction to sesame within the last year. A high Skin prick tests (SPT) wheal size alone was not sufficient to diagnose sesame allergy. Only patients ≥3.7 y/o were eligible for sesame-OIT while there was no age limitation for diagnostic-OFC. Patients' evaluation included a comprehensive general medical history as well as previous reactions to sesame. SPT for house dust mite and for sesame were performed. Due to the high rate of false negative results obtained using commercial SPT extracts, a validated high protein (100 mg/mL) sesame extract (HPSE) was used for SPT, as previously described.[32–34] All patients aged ≥5 years underwent spirometry (Minispir, Mir, Rafamedical, Yavne, Israel), with or without a bronchodilator, before OFC. Patients with any concurrent illness or with uncontrolled asthma were not challenged, and those with active eosinophilic gastrointestinal or autoimmune diseases were excluded from OIT. Patients with past severe anaphylactic reactions were not excluded from both diagnostic-OFC or OIT-OFC.

2.2 | Sesame challenge protocols

The diagnostic-OFC protocol, included a single day with nine increasing doses and gradually increasing intervals from 15 to 60 min (Table S1). For technical reasons, the diagnostic-OFC protocol underwent a slight change in 2017 where the first two doses changed from 0.3 and 3 mg protein to 0.1 and 5 mg protein, respectively. Doses of less than 240 mg sesame protein were prepared from a low-fat, high protein (46%) sesame flour (Sukrin) which was dissolved in water to a concentration of 100 mg/mL of protein.[33,34] The low-fat content reduces the risk of delayed absorption and late reactions during OIT. Doses of 240–4000 mg protein were given as raw Tahini, containing 100% sesame. The OIT-OFC was performed in clinic and spanned over the first 2–3 days of OIT to determine each patients' single highest tolerated dose, SHTD,[32] (Table S2, Days 1–3). This protocol included longer time intervals between doses, so that a maximal dose of 120 mg sesame protein was initially reached on the first day. The second day served to reach the highest dose of 4800 mg. This protocol also underwent a modification in 2017 where the maximal dose reached on the first day was 40 mg, on the second day 240 mg, and the third day served to reach the highest dose. This protocol adjustment was intended to improve patient safety. While in the initial protocol dose escalation on the first day was of higher magnitude and 2–3 days were required to accurately determine NOAEL and LOAEL, the new protocol included modest dose escalation, especially on the first day, and the NOAEL and LOAEL were typically identified in 1–2 days, with milder reactions. Both protocols eventually led to accurate identification of patients' eliciting dose. Patients who reached the highest dose with no reaction were classified as nonallergic and were excluded from OIT and from this study. In case of a reaction, the protocol on the following days included gradual administration of the doses to which there was no reaction. Afterwards, a final challenge day (Table S2, Day 4) which included two repeated administrations of the previous days' NOAEL dose with long time intervals, 90–120 min, for minimizing the risk of dose accumulation, was performed. This challenge was designated to validate the safety of patients' SHTD. Patients who reacted to doses >240 mg protein were finally challenged to a maximal dose of 240 mg as this was the highest starting dose of the treatment for safety reasons. Patients were then guided to take the determined SHTD daily at home. All OFCs were performed under medical supervision and an accurate documentation of the protein amount and of the timing of dose administration, timing and type of subjective and objective symptoms, and treatments given, was performed throughout the OFCs.[35] Allergic reactions during OFCs were analyzed according to CoFAR grading version 3.0 scale for systemic allergic reactions in food allergy.[36] Contact urticaria was categorized as a subjective symptom in the analysis. For both diagnostic-OFC and OIT-OFC protocols, all objective signs and symptoms (except for contact urticaria), and persistent (more than 15 min) or severe abdominal pain, were considered as a reaction, treated accordingly, and led to cessation of the challenge. In the case of subjective symptoms, and transient mild or moderate abdominal pain, the next dose was postponed, until symptoms resolved, but such symptoms were not an indication to stop dose increases.

Patients remained under medical supervision for at least 90 min after either the last uneventful dose administration, or symptoms relief in case of a reaction.

2.3 | Data collection and statistical analysis

NOAEL and LOAEL values obtained, according to previously published methodology,[37] from both diagnostic-OFC and OIT-OFC were identified and analyzed. In addition, for each individual who have undergone OIT, the single highest tolerated dose (SHTD) at the beginning of OIT, was determined. The final challenges confirming the SHTD for each patient were analyzed as safe-dose OFCs. Results of diagnostic-OFC and of OIT-OFC were analyzed separately and in combination. For patients with >1 positive challenge, either >1 diagnostic-OFC, or a diagnostic-OFC and an OIT-OFC challenge, only the first challenge was included in the statistical analysis. For patients who reacted both in the first and the second OIT-OFC days, only the NOAEL and the LOAEL identified on the second day were included in the analysis. The data were analyzed utilizing Bayesian stacked parametric survival methods with frailty components and interval-censored failure times developed by Wheeler et al., 2021.[38] This approach combines five parametric survival distributions (Weibull, Log-Gaussian (or Log-Normal), Log-Logistic, Generalized Pareto, and Log-Laplace (or Log-Double-Exponential) into a single model averaging threshold-dose distribution curve that was used to determine population ED values on the basis of both discrete dosing and cumulative dosing. Further details of the methodology and the applied software can be found in Remington et al. and Wheeler

et al.[8,38] Chi test and the Mann Whitney test were used to compare categorical and numerical variables, respectively, between groups.

3 | RESULTS

3.1 | Reaction thresholds in the entire population

Threshold dose distributions for the entire cohort were calculated for 250 patients who underwent a diagnostic-OFC or an OIT-OFC. Median age was 6.9 years, most were males and nearly half were asthmatics (Table 1). A diagnostic-OFC was performed in 140 patients, but 13 had insufficient information, and the remainder 127 patients were included in the threshold analysis. OIT-OFCs were performed in 123 patients during the study period (additional 27 OIT-OFCs performed following a diagnostic-OFC were not included in the threshold analysis). The characteristics of diagnostic-OFC and OIT-OFC patients are detailed in Table S3. The eliciting dose distribution curves of the entire population, using the model averaging method, for discrete and cumulative values, are presented in Figure 1A,B, respectively. The discrete and cumulative protein amounts estimated to elicit an objective reaction in 1% of the population, ED01, were 0.8 mg (range 0.3–6.3) and 0.7 mg (range 0.1–7.1), respectively, and those for 5% of the population, ED05, were 3.4 mg (range 1.2–20.6) and 4.5 mg (range 1.2–28.8), respectively (Table 2).

We next examined whether patients' background parameters, including age at OFC day, gender, asthma, atopic dermatitis and allergy to multiple foods, or parameters of allergy severity, including SPT wheal size and a history of previous epinephrine treated reactions to sesame affect the threshold of reaction to sesame (Figure S1). None of these parameters was found to significantly impact reaction thresholds. However, comparison of the two OFC groups showed that reactions were elicited by significantly lower median doses during OIT- compared to diagnostic-OFCs (Table 3). The threshold distribution curves of the individual OFC groups also show that the OIT population generally reacted at lower doses (Figure S2). However, the confidence intervals of both threshold distribution curves show a great overlap, indicating that the differences are not statistically significant. Importantly, the lowest doses eliciting objective reactions was similar in the two groups (3 mg in the diagnostic- and 2.5 mg in the OIT-OFC group).

Twenty-four patients had two positive diagnostic-OFCs, additional four patients had three, and one patient had four positive diagnostic-OFCs to sesame during the study period. Repeated OFCs

TABLE 1 Characteristics of the study population and of the 158 patients of them who were also challenged according to the safe-dose protocol.

Parameter	All patients ($n=250$)	Safe-dose OFC ($n=158$)
Age, years[a]	6.9 (4.9–11.2), [0.6–40.7]	7.5 (5.9–10.8), [3.9–27.1]
Male gender	167 (63.7%)	99 (62.6%)
SPT wheal size (mm)	5 (4–7), [0–21]	5 (4–7), [0–21]
SPT extract wheal size (mm)[a]	8 (6–11), [1–28]	8 (6–12), [1–28]
Past epinephrine for reaction to sesame	59 (22.5%)	51 (32.3%)
Asthma	118 (45%)	77 (48.7%)
Atopic dermatitis	162 (61.8)	112 (70.9%)

[a] median (IQR) [Range].

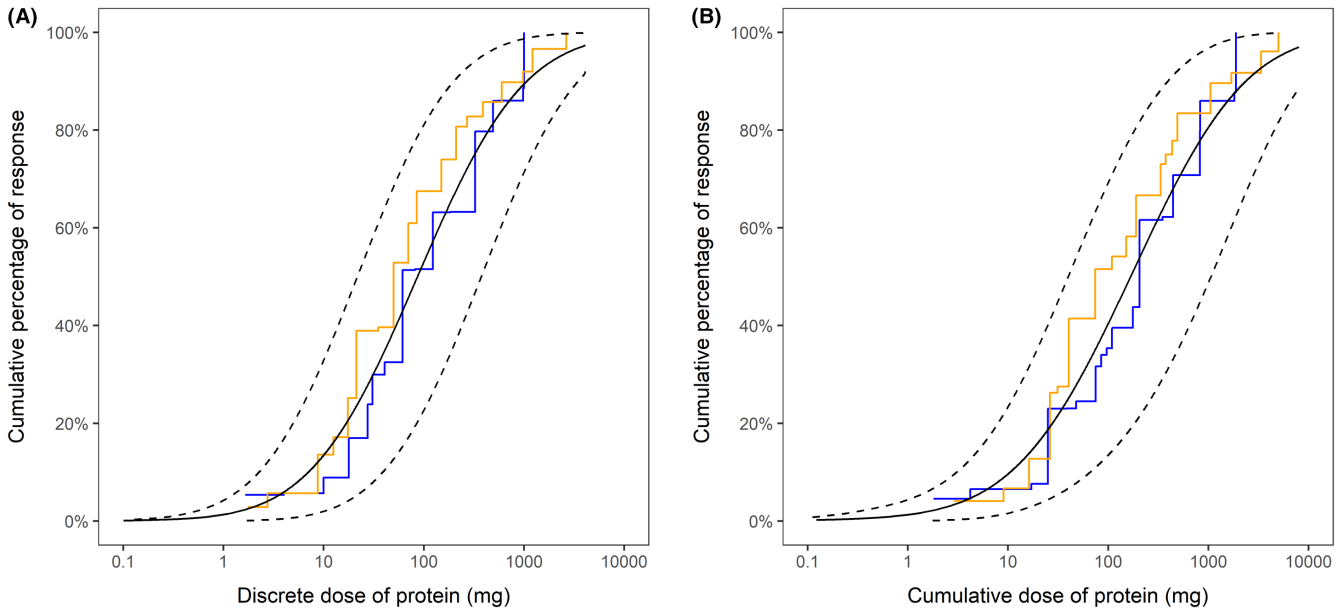


FIGURE 1 Model average threshold distribution curves for objective symptoms in the study population, based on the discrete (A) and cumulative (B) doses of protein. The total dataset is separated into the diagnostic-OFC (blue Kaplan–Meier curve, $n=127$) and OIT-OFC (orange Kaplan–Meier curve, $n=123$) subgroups.

TABLE 2 Estimated eliciting doses for objective symptoms in sesame for the entire population ($n = 250$) and for the patients challenged for safe-dose verification.

	All patients ($n = 250$)		Safe-dose OFC ($n = 158$)
ED value	Discrete doses (mg protein)	Cumulative doses (mg protein)	Discrete doses (mg protein)
01	0.8 (0.3–6.3)	0.7 (0.1–7.1)	0.8 (0.4–7.5)
05	3.4 (1.2–20.6)	4.5 (1.2–28.8)	3.4 (1.2–22.9)
10	7.0 (2.3–39.0)	10.5 (3.1–66.2)	6.9 (2.2–41.6)
25	23.3 (6.6–114.2)	39.8 (11.1–266.3)	21.7 (6.1–112.9)
50	86.3 (21.7–374.6)	167.0 (39.9–1060)	76.1 (18.7–343.6)

TABLE 3 Objective and subjective[a] sesame reaction thresholds in study patients.

Outcome	Diagnostic-OFC ($n = 127$)	OIT-OFC ($n = 150$[b])	SAFE-OFC ($n = 158$)
Objective reaction dose Discrete (mg protein) Median, IQR Mean, range	240, 60–480 596.2, 3–4000	60, 30–120 380.9, 2.5–4080	No objective reaction
Objective reaction dose-cumulative (mg protein) Median, IQR Mean, range	348.3, 85–992 954.6, 3.3–5828	127, 30–300 727, 4.1–7680	No objective reaction
Subjective reaction dose-discrete (mg protein) Median, IQR Mean, range	20, 5–60 50.22, 0.1–480	10, 1–40 84.15, 0.1–1920	30, 10–80 79.7, 0.5–1000
Subjective reaction dose-cumulative (mg protein) Median, IQR Mean, range	25, 5–65 79.9, 0.1–833	19.1, 1.6–40136.2, 0.1–3100	75, 10–200 105, 0.6–1500
Time from OIT start to subjective symptoms (min) Median, range	22, 0–193	19, 0–194	0, 0–185
Time between subjective and objective symptoms (min) Median, range	100, 18–327	126, 26–312	No objective symptoms

[a] Subjective symptoms were present in 63 (50.4%) diagnostic-OFCs, 77 (52%) OIT- OFCs and 31 (19.5%) safe-dose OFCs.

[b] OIT-OFCs performed after a diagnostic-OFC are also included.

were typically performed for identification of spontaneous recovery. Naturally, in the case of recovery, negative OFCs were not included in the analyses. Twenty-three patients had an OIT-OFC following a diagnostic-OFC and additional four were challenged by OIT-OFC after two diagnostic-OFCs. Time intervals between each two adjacent challenges varied between 6 months and 6 years. Overall, there were 46 patients with two, eight patients with three, and one patient with four OFC positive results (Figure S3). While the size of this group does not enable to draw firm conclusions, ~50% of the patients who remained with sesame allergy experienced an increase in the reaction threshold of up to 17-fold and ~ 50% had a decreased reaction threshold of up to 43-fold over time. The individual log-fold change in the threshold was between −1.6 and 1.2, but when considering all patients together, the log-fold change was practically 0.

Overall, a total of 324 positive OFCs (155 diagnostic- and 169 OIT-OFCs) and additional 158 safe-dose challenges were performed during the study period. Information regarding reactions' grading, organ system involved and treatment provided are detailed in Table S4. Most reactions were mild (grade I-II) in both diagnostic-OFCs and OIT-OFCs, which were performed by the same medical staff, but the former required more epinephrine treatments. In addition, the rate of reactions involving the skin and the respiratory tract was significantly higher, and the rate of those involving gastrointestinal symptoms was significantly lower in the diagnostic-OFC, comparing to OIT-OFC ($p = .01$, $p = .032$, $p = .006$ respectively).

3.2 | Reaction threshold to safe-dose OFCs

A total of 158 patients underwent a safe-dose challenge and their characteristics are detailed in Table 1. In the case of 13 patients, OIT

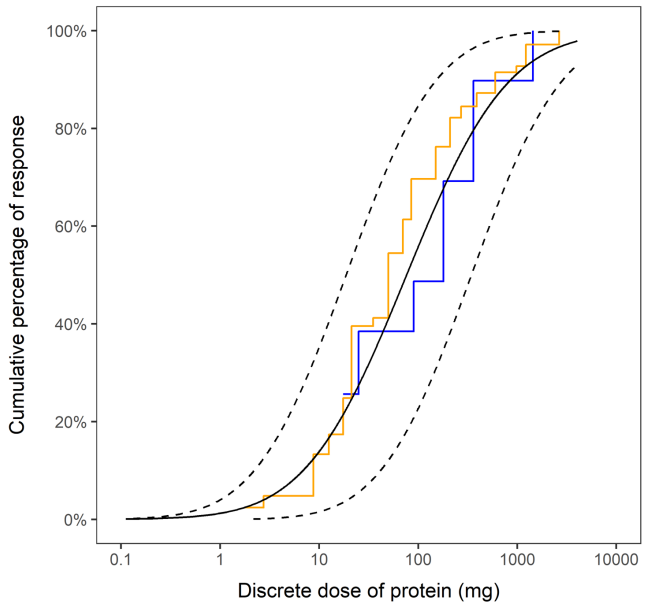


FIGURE 2 Model average threshold distribution curve for objective symptoms in the sesame "safe-dose" group. The total dataset is separated into patients challenged for "safe dose" shortly after a diagnostic-OFC (blue Kaplan–Meier curve, $n = 13$) and those challenged after an OIT-OFC (orange Kaplan–Meier curve, $n = 145$) subgroups.

was initiated shortly after a diagnostic-OFC which provided us with an estimated threshold. The safe dose was examined and verified according to the results of this OFC. The analysis of the threshold distribution according to safe-dose OFCs was performed separately for these 13 patients and for the other 145 patients (Figure 2). Specific EDs that were extrapolated from the model are listed in Table 2. Both the ED01 (0.8 mg, 0.4–7.5), and the ED05 (3.4 mg, 1.2–22.9) of all 158 patients who underwent a safe-dose challenge were comparable to the entire cohort of 250 patients. The safe dose was 1 mg in 100% and 2.5 mg in 95% of the safe-dose OFCs (Table 4).

3.3 | Subjective symptoms during oral food challenges

Subjective symptoms were not a reason for OFC termination but could lead to prolongation of the dosing interval.[35] The rate of such symptoms was similar in diagnostic-OFC (50.4%) and OIT-OFC (52%) but significantly lower (19.5%) during safe-dose challenges. Oral symptoms were the most frequent subjective symptoms in all types of OFCs followed by transient gastrointestinal symptoms (Table S5). Discrete median (IQR) doses eliciting subjective symptoms were 20 mg (5–60) for diagnostic-, 10 mg (1–40) for OIT-, and 30 mg (10–80) for safe-OFCs (Table 3). In comparison, the doses eliciting objective symptoms were significantly higher, median (IQR) 240 mg (60–480) for diagnostic- compared to 60 (30–120) for OIT-OFC (Table 3). The median (range) time interval between subjective symptoms and objective signs was 100 min (18–327) and 126 min (26–312) for diagnostic-OFCs and OIT-OFCs, respectively.

TABLE 4 Actual doses verified as safe among the 158 patients who were challenged by the sesame safe-dose OFCs.

Safe dose, SD, in a percentage of the population	Sesame mg protein
SD 100	1 mg
SD 95	2.5 mg
SD 90	5 mg
SD 75	10 mg
SD 50	40 mg

Of the 250 patients studied, 27 (10.8%) reported subjective symptoms to doses ≤1 mg sesame protein during 29 OFCs (six during diagnostic-OFC, 20 during OIT-OFC, and three during safe-dose OFCs). (Table S6). All reported symptoms consisted of oral pruritus. In 23 of the 29 cases, the symptoms disappeared within a few minutes and the following dose was administered without delay, in five cases there was a delay of up to 10 min in administration of the following dose, and in a single case a significant interval of 66 min was documented, likely reflecting a technical error. The doses that elicited objective symptoms during the same challenges were significantly higher (5–800 times), and there was no objective reaction in any of the challenges, including the safe-dose OFCs, to a dose of ≤1 mg sesame protein (Table 3).

4 | DISCUSSION

The current study presents distribution curves of reaction thresholds to sesame using the largest population with no left censors studied thus far. It also confirms the results by using a safe-dose OFC protocol with long intervals between doses. This study adds important information to the growing data on sesame thresholds and its results could assist in determining sesame safe doses for risk management across the food industry and supply chain.

The recent addition of sesame to the list of allergenic foods which require labeling in the United States, has prompted the need for reliable information on sesame reaction threshold at a population level. However, most of these studies are limited by small sample sizes (up to 40 patients), inclusion of OFCs with right (subjective symptoms) or left (reaction to the first dose) censors, and the accurate protein amount is not always specified. Turner et al[31] have combined data on 246 sesame OFCs from 11 studies and found that the discrete ED01 and ED05 were 0.2 mg and 2.4 mg, respectively, and that the cumulative ED01 and ED05 were 0.2 mg and 2.5 mg, respectively. Limiting the analysis to double-blind placebo-controlled food challenges (DBPCFCs) only did not significantly change the results,[31] supporting the use of open OFCs in this type of studies. However, analyzing data from 172 OFCs, after excluding studies with significant left censoring, nearly doubled the threshold to 0.4 mg and 3.8 mg for discrete ED01 and ED05, respectively, and to 0.4 mg and 4.2 mg for cumulative ED01 and ED05, respectivly. Our study involved the largest population

(250 OFCs) without censoring. The protocols included low starting and high maximal doses, all doses had accurate protein content, and the diagnosis was based on objective symptoms or prolonged abdominal pain only. In addition, high-risk patients were included and challenged as well. The levels of ED01 and ED05 for both discrete (0.8 mg and 3.4 mg, respectively) and cumulative (0.7 mg and 4.5 mg, respectively) doses are comparable to the study by Turner et al, after the removal of the studies with a significant number of left censors,[31] supporting the validity of the data.

Oral immunotherapy (OIT) for food allergy is performed, in recent years, in a growing number of centers, using various protocols.[39] Some OIT programs require a positive OFC before starting treatment, thereby providing information on eliciting doses in their patients. The OIT protocol at Shamir Medical Center explores patients' eliciting doses and individualized highest tolerated dose at the beginning of treatment, and is different from the protocol used for a diagnostic-OFC.[32] We found lower EDs in OIT- compared to diagnostic-OFCs. The 123 patients whose OIT-OFCs were analyzed had characteristics of a more severe food allergy (older age, increased atopic traits, higher SPT levels to sesame, and significantly more previous epinephrine-treated reactions to sesame) compared to the 127 diagnostic-OFC group, and this may account for the lower EDs observed in these patients. Of note, the additional analysis we performed, showed that the ED is not affected by any parameter (demographic or clinical). The differences in EDs could also potentially reflect the different OFC protocols. However, the lowest doses eliciting reactions were comparable between the two groups, supporting the concept that differences in protocols are covered by random effects in the model averaging method.

This study also provides an opportunity to evaluate the eliciting doses in 158 patients who underwent specialized safe-dose OFCs, the importance of which lies in complete elimination of the effect of dosing intervals and dose accumulation. This is primarily important for establishing a valid ED05, as the recent Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens[30] suggested that the safety objective ED would be met by starting the definition of range of envisioned Reference Doses (RfD) at the ED05 and rounding its values down to one significant figure. A RfD of 2.0 mg sesame protein was recommended by the FAO/WHO Expert Consultation[30] which matches well with the ED05's found in our study and the study from Turner et al.[31]

Previous studies found a higher ED05 in safe-dose OFCs compared to the estimated value obtained by analysis of diagnostic-OFCs,[12,13] likely due to left censoring in the latter. This is further supported by the study of Turner et al showing a discrete ED05 of 2.4 mg with left censors and of 3.8 mg when studies with significant left censors were excluded.[31] The ED05 derived from our analysis of safe-dose OFCs and diagnostic-OFCs, which had no left censors, were comparable. Together, this data suggests that data generated by diagnostic and OIT-OFCs provide a validated population ED05 that can be used for risk assessment and risk management purposes in the food industry, and further optimization can be achieved by minimizing left censors. The safe-dose OFCs also provide data, not only on estimated reaction doses but also on actual safe doses in the population. All 158 patients who underwent a safe-dose OFC (202 patients, updated for 12/2022) could tolerate ≤1 mg sesame protein and 95% could tolerate a dose of 2.5 mg.

Subjective symptoms, although not necessarily indicating an actual reaction,[35,40] may be stressful. Naturally, it is of interest for the food industry not only to verify food safety but also a perception of safety for the customers.[41] In this study, there was no safe dose in terms of subjective symptoms as 27 patients reported subjective symptoms to doses ≤1 mg sesame protein. Importantly, subjective symptoms to <1 mg sesame protein were experienced by only 10% of patients, and the symptoms were restricted to the oral cavity, and were mild and short-lived. Of note, these patients underwent open OFCs and were therefore aware that they were consuming the allergenic food.[42] Also, the doses contained sesame protein alone without any food matrix which might mask the oral discomfort. It can be assumed that in real life, the presence of food matrix and the blinding to the presence of the allergen, would reduce the frequency for subjective symptoms to minimal doses.

This study had several limitations. First, it represents only an Israeli population, which is unique in its exposure to Mediterranean diet including sesame, and might not apply for other populations. However, the fact that the ED values obtained here are in agreement to the values reported in other populations, is reassuring. Second, this study does not include DBPCFC, although as discussed, open challenges were shown to reliably reflect threshold distributions for milk at a population level.[13] Third, although this study includes a large number of patients, a precise estimation of ED01 values is limited, because even with 250 patients only two or three patients are expected to react at the ED01 level, which was not the case in our study. Another potential limitation is potential acquisition of tolerance during several days of OIT-OFCs. This risk is minimized by the fact that OIT-OFCs are characterized by large intervals between doses, and that the final safe dose is confirmed on a separate day. Also, the use of a low-fat sesame flower could have impacted the ED estimation due to lower quantity of oleosins. However, as the storage protein ses i 1 is considered the main sesame allergen,[43] in oppose to oleosins which were demonstrated as minor allergens,[44] this effect is likely negligible. Finally, safe doses were analyzed in patients older than 3.7 y/o only, as this was the age limit for starting OIT. An older age was previously shown to pose a higher risk of a low cumulative threshold dose of an allergic reaction.[45] Thus, inclusion of younger children might have resulted in higher thresholds.

In summary, this study provides information regarding both the reaction thresholds and the safe doses of sesame in a large group of allergic patients. These results provide additional support regarding the effectiveness of current research methods in the evaluation of reaction thresholds for allergenic foods, as well as important data for the risk assessment and risk management of sesame within food business operations.

AUTHOR CONTRIBUTIONS

Liat Nachshon and Arnon Elizur contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting the article. Michael Levy, Michael Goldberg, Naama Epstein-Rigbi, and Yitzhak Katz contributed to acquisition of data, analysis and interpretation of data, and drafting the article. Joost Westerhout, Marty Blom, and Benjamin Remington contributed to analysis and interpretation of data, and drafting the article.

ACKNOWLEDGMENTS

We would like to thank Tehila Abergil and Keren Golobov for assisting with patient data collection.

FUNDING INFORMATION

Dr. Goldberg is funded by a Kamea grant from the Ministry of Health, Israel. Professor Katz is supported by the Leon Alcalay Chair in Pediatric Immunology, Tel Aviv University.

CONFLICT OF INTEREST STATEMENT

All authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Liat Nachshon https://orcid.org/0000-0003-4377-472X
Benjamin Remington https://orcid.org/0000-0001-5450-8334
Michael R. Goldberg https://orcid.org/0000-0003-1355-1533
Naama Epstein-Rigbi https://orcid.org/0000-0001-5321-1782
Arnon Elizur https://orcid.org/0000-0001-8157-8143

REFERENCES

1. Allen KJ, Turner PJ, Pawankar R, et al. Precautionary labelling of foods for allergen content: are we ready for a global framework? *World Allergy Organ J*. 2014;7:1-14.
2. The food allergen labeling and consumer protection act of 2004 (FALCPA), Public Law 108–282—AUG. 2004 https://www.fda.gov/food/food-allergensgluten-free-guidance
3. Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25. Chapter IV, mandatory food information section 1, Content and presentation, Article 9 List of mandatory particulars. 2011 https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:304:0018:0063:en:PDF
4. Gern JE, Yang E, Evrard HM, Sampson HA. Allergic reactions to milk-contaminated nondairy products. *N Engl J Med*. 1991;324:976-979.
5. Zurzolo GA, Allen KJ, Peters RL, et al. Self-reported anaphylaxis to packaged foods in Australia. *J Allergy Clin Immunol Pract*. 2019;7:687-689.
6. Taylor SL, Hefle SL, Bindslev-Jensen C, et al. A consensus protocol for the determination of the threshold doses for allergenic foods: how much is too much? *Clin Exp Allergy*. 2004;34(5):689-695.
7. Crevel RWR, Baumert JL, Baka A, et al. Development and evolution of risk assessment for food allergens. *Food Chem Toxicol*. 2014;67:262-276.
8. Remington BC, Westerhout J, Meima MY, et al. Updated population minimal eliciting dose distribution for use in risk assessment of 14 priority food allergens. *Food Chem Toxicol*. 2020;139:111259.
9. Allen KJ, Remington BC, Baumert JL, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J Allergy Clin Immunol*. 2014;133:156-164.
10. Bird A, Leonard S, Groetch M, et al. Conducting an OFC: an update to the 2009 adverse reactions to foods committee work group report. *J Allergy Clin Immunol Pract*. 2020;8:75-90.
11. Blumchen K, Beder A, Beschorner J, et al. Modified oral food challenge used with sensitization biomarkers provides more real-life clinical thresholds for peanut allergy. *J Allergy Clin Immunol*. 2014;134:390-398.
12. Hourihane JO, Allen KJ, Shreffler WG, et al. Peanut allergen threshold study (PATS): novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy. *J Allergy Clin Immunol*. 2017;139:1583-1590.
13. Turner PJ, d'Art YM, Duca B, et al. Single-dose oral challenges to validate eliciting doses in children with cow's milk allergy. *Pediatr Allergy Immunol*. 2021;32(5):1056-1065.
14. Turner PJ, Patel N, Ballmer-Weber BK, et al. Peanut can be used as a reference allergen for hazard characterization in food allergen risk management: a rapid evidence assessment and meta-analysis. *J Allergy Clin Immunol Pract*. 2022;10(1):59-70.
15. Gangur V, Kelly C, Navuluri L. Sesame allergy: a growing food allergy of global proportions? *Ann Allergy Asthma Immunol*. 2005;95:4-11.
16. Efrati I. Tourist dies of allergic reaction to tahini. https://www.haaretz.com/tourist-dies-after-eating-tahini-1.5243639
17. Guardian: Preat A Manger and BA face questions over girl's allergy death on plane. https://www.theguardian.com/society/2018/sep/23/pret-a-manger-british-airways-questions-allergy-girl-inquest
18. Gendel SM. Comparison of international food allergen labeling regulations. *Regul Toxicol Pharmacol*. 2012;63:279-285.
19. Food Allergies. FDA. https://www.fda.gov/food/food-labeling-nutrition/food-allergies
20. Purington N, Chinthrajah RS, Long A, et al. Eliciting dose and safety outcomes from a large dataset of standardized multiple food challenges. *Front Immunol*. 2018;21(9):2057.
21. Dano D, Remington BC, Astier C, et al. Sesame allergy threshold dose distribution. *Food Chem Toxicol*. 2015;83:48-53.
22. Kanny G, Hauteclocque CD, Moneret-Vautrin DA. Sesame seed and sesame seed oil contain masked allergens of growing importance. *Allergy*. 1996;51:952-957.
23. Leduc V, Tzen JTC, Morisset M, Guerin L, Kanny G. Identification of oleosins as major allergens in sesame seed allergic patients. *Allergy*. 2006;61(3):349-356.
24. Brough HA, Caubet JC, Mazon A, et al. Defining challenge-proven coexistent nut and sesame seed allergy: a prospective multicenter European study. *J Allergy Clin Immunol*. 2020;145(4):1231-1239.
25. Salari F, Bemanian MH, Fallahpour M, et al. Comparison of diagnostic tests with Oral food challenge in a clinical trial for adult patients with sesame anaphylaxis. *Iran J Allergy Asthma Immunol*. 2020;19(1):27-34.
26. Chan JCK, Peters RL, Koplin JJ, et al. Food challenge and community-reported reaction profiles in food-allergic children aged 1 and 4 years: a population-based study. *J Allergy Clin Immunol Pract*. 2017;5(2):398-409.e3.
27. Yanagida N, Ejiri Y, Takeishi D, et al. Ses i 1-specific IgE and sesame oral food challenge results. *J Allergy Clin Immunol Pract*. 2019;7(6):2084-2086.e4.
28. Saf S, Sifers TM, Baker MG, et al. Diagnosis of sesame allergy: analysis of current practice and exploration of sesame component Ses i 1. *J Allergy Clin Immunol Pract*. 2020;8(5):1681-1688.e3.
29. Ovadia A, Yoffe S, Orr YB, Tasher D, Dalal I. Sesame-allergic patients can tolerate intact sesame seeds food challenge. *J Allergy Clin Immunol Pract*. 2022;10(1):336-338.

30. Food and Agricultural Organization of the United Nations/World Health Organization. FAO and WAO. Risk assessment of food allergens- part 2: review and establish threshold levels in foods for the priority of allergens. Meeting Report Food Safety and Quality Series No. 15. Rome. 2022. doi:10.4060/cc2946en Accessed April, 2023.
31. Turner PJ, Gretzinger M, Patel N, et al. Updated threshold dose-distribution data for sesame. *Allergy*. 2022;77:3124-3162.
32. Nachshon L, Goldberg MR, Levy MB, et al. Efficacy and safety of sesame oral immunotherapy–a real-world, single center study. *J Allergy Clin Immunol Pract*. 2019;7(8):2775-2781.
33. Appel M, Nachshon L, Elizur A, Levy MB, Katz Y, Goldberg MR. Evaluation of the basophil activation test and skin prick testing for the diagnosis of sesame food allergy. *Clin Exp Allergy*. 2018;48(8):1025-1034.
34. Goldberg MR, Appel MY, Nachshon L, et al. Combinatorial advantage of Ses i 1-specific IgE and basophil activation for diagnosis of sesame food allergy. *Pediatr Allergy Immunol*. 2021;32(7):1482-1489.
35. Nachshon L, Zipper O, Levy MB, Goldberg MR, Epstein-Rigby N, Elizur A. Subjective oral symptoms are insufficient predictors of a positive oral food challenge. *Pediatr Allergy Immunol*. 2021;32(2):342-348.
36. Chinthrajah RS, Jones SM, Kim EH, et al. Updating the CoFAR grading scale for systemic allergic reactions in food allergy. *J Allergy Clin Immunol*. 2022;149:2166-2170.
37. Westerhout J, Baumert JL, Blom WM, et al. Deriving individual threshold doses from clinical food challenge data for population risk assessment of food allergens. *J Allergy Clin Immunol*. 2019;144(5):1290-1309.
38. Wheeler MW, Westerhout J, Baumert JL, Remington BC. Bayesian stacked parametric survival with frailty components and interval-censored failure times: an application to food allergy risk. *Risk Anal*. 2021;41(1):56-66.
39. Perrett K, Sindher S, Begin P, Shanks J, Elizur A. Advances, practical implementation and unmet needs regarding oral immunotherapy for food allergy. *J Allergy Clin Immunol Pract*. 2022;10(1):19-33.
40. Turner PJ, Patel N, Blumchen K, Berkes S, Sampson HA, Beyer K. Impact of using less objective symptoms to define tolerated dose during food challenges: a data-driven approach. *J Allergy Clin Immunol*. 2023;152:145-154.
41. Turner PJ, Baumert JL, Beyer K, et al. 'Too high, too low': the complexities of using thresholds in isolation to inform precautionary allergen ('may contain') labels. *Allergy*. 2022;77(6):1661-1666.
42. Remington BC, Westerhout J, Dubois AEJ, et al. Suitability of low-dose, open food challenge data to supplement double-blind, placebo-controlled data in generation of food allergen threshold dose distributions. *Clin Exp Allergy*. 2021;51(1):151-154.
43. Maruyama N, Nakagawa T, Ito K, et al. Measurement of specific IgE antibodies to Ses i 1 improves the diagnosis of sesame allergy. *Clin Exp Allergy*. 2016;46(1):163-171.
44. Ehlers AM, Rossnagel M, Brix B, et al. Sesame oleosins are minor allergens. *Clin Transl Allergy*. 2019;28(9):32.
45. Cottel N, Saf S, Bourgoin-Heck M, et al. Two different composite markers predict severity and threshold dose in peanut allergy. *J Allergy Clin Immunol Pract*. 2021;9(1):275-282.e1.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Nachshon L, Westerhout J, Blom WM, et al. Sesame eliciting and safe doses in a large sesame allergic population. *Allergy*. 2023;00:1-9. doi:10.1111/all.15863