Communications

Comparison of an FDA-approved peanut oral immunotherapy product with peanut food products

Key words: *Content variability, oral immunotherapy, peanut allergens, peanut protein, FDA-approved peanut* (Arachis hypogaea) *allergen powder-dnfp*

Abbreviations used
FDA: US Food and Drug Administration
OIT: Oral immunotherapy
PTAH: Peanut *(Arachis hypogaea)* allergen powder-dnfp
RSD: Relative SD

To the Editor:

IgE-mediated food allergy, particularly peanut allergy, has become an increasing concern worldwide, especially in Western countries. In the United States, the self-reported prevalence of food allergy is at least 10%,[1] with peanut *(Arachis hypogaea)* allergy affecting approximately 2% of the pediatric population.[2] Peanut allergy is a potentially life-threatening condition, as accidental ingestion frequently leads to anaphylaxis,[3] and although fatalities are rare, they continue to occur. Unlike food allergies to milk or egg, which are more likely to resolve without intervention, peanut allergy often progresses during early childhood and persists into adulthood.[2]

Given the growing unmet need, diagnostic oral challenges and immunotherapy, including oral immunotherapy (OIT),[2] sublingual immunotherapy,[4] and epicutaneous immunotherapy,[5] have been areas of intense interest. Of these, only OIT with peanut *(Arachis hypogaea)* allergen powder-dnfp (PTAH) has been approved in the United States[6] and European Union for children aged 1 to 17 years who have peanut allergy. However, OIT is sometimes conducted using grocery store–sourced peanut products not developed for medical use. Unlike PTAH, these off-the-shelf products are not standardized in terms of protein content or specific allergen composition, posing potential safety concerns, particularly because some peanut OIT protocols typically begin with doses of peanut protein lower than 1 mg.[7] Differences between the allergen profiles of peanut-containing foods and the effect of roasting have previously been reported.[8] In this study, we assessed the variability of peanut-containing foods in terms of total protein content and allergen content, comparing them with PTAH. We evaluated 7 categories of products that are commonly used for peanut OIT, comparing their content across 5 lots each. These were PTAH, peanut kernels, peanut butter, freeze-dried peanut butter, freeze-dried peanut kernels, peanut-containing candies, and peanut-containing puffs, which are available either in the United States or in both the United States and the European Union. Total proteins were measured using the Kjeldahl method directly on the product. For quantification of specific Ara h 1, Ara h 2, Ara h 3, Ara h 6, and Ara h 8 allergens using mAb-based ELISA 2.0, as per the manufacturer's instructions (InBio, Charlottesville, Va), the products were extracted in 2.5% (wt/vol) sodium bicarbonate, 0.1 M, pH 9.6, for 24 hours at $+5°C \pm 3°C$. In the case of peanut-containing candies, extraction was performed after removal of the chocolate coating.

The peanut protein content varied from 113 mg/g to 478 mg/g of product, demonstrating up to a 4-fold variation in peanut protein between products (Fig 1 and Table I). The lot-to-lot variation of protein content within the different food products (relative SD [RSD]) ranged from 2% to 18%, whereas the RSD for PTAH was 1% (Table I).

Product-to-product variation in the mean component allergen contents ranged from 9-fold (Ara h 8) to 767-fold (Ara h 1) (Fig 1 and Table I). As for the lot-to-lot variation in component allergen content within each food product, the maximum RSD ranged from 36% to 196%. In contrast, the RSD was among lots of PTAH consistently less than 22%, regardless of the allergen component considered (Table I).

It is also worth noting that although the peanut-containing candies originating from the United States and European Union were of the same commercial brand, they displayed marked differences in both the variability of their protein content and their concentrations of specific peanut allergens (Fig 1 and Table I).

According to the US Food and Drug Administration (FDA), "when used in OIT to treat allergic individuals, products traditionally considered foods are classified as biologics and regulated by the FDA's Center for Biologics Evaluation and Research…"[6] As a result, before undergoing pivotal clinical trials to assess safety and efficacy, PTAH required the submission of an investigational new drug application. This process mandates manufacturing in compliance with current good manufacturing practice and establishment of chemistry, manufacturing, and control parameters along with corresponding specifications. The investigational new drug process is designed to ensure product safety and efficacy, including maintaining the purity and potency of the drug substance across different manufacturing batches. During PTAH production, most batches of peanut flour sourced from the Golden Peanut and Tree Nut Company (Alpharetta, Ga) are rejected for failing to meet the required potency levels of Ara h 1, Ara h 2, and Ara h 6 or for being contaminated with aflatoxin.[9] It is therefore not surprising that PTAH demonstrated the least variation across all parameters analyzed in our study. We did not evaluate the clinical relevance of our findings, although because allergic adverse events with peanut OIT are anticipated and common, it is reasonable to speculate that using an FDA-approved product may be safer and potentially more effective than using a peanut food product, especially in the early phases of treatment of highly sensitive patients.

The observed variability in protein and component contents of off-the-shelf products could lead to both underdiagnosis and overdiagnosis of peanut allergy when used in oral food challenges owing to the unpredictable variation in peanut allergen content that could present as "cold" lots versus "hot" lots.[10] Although currently there are no commercially available products with a standardized allergen content, use of such products in the future would allow standardized challenges that keep allergen content within a "target zone," allowing higher consistency and comparability of results within the same patient and among different patients.[10] Furthermore, use of nonstandardized products could be one factor that could increase the risk of OIT and adverse

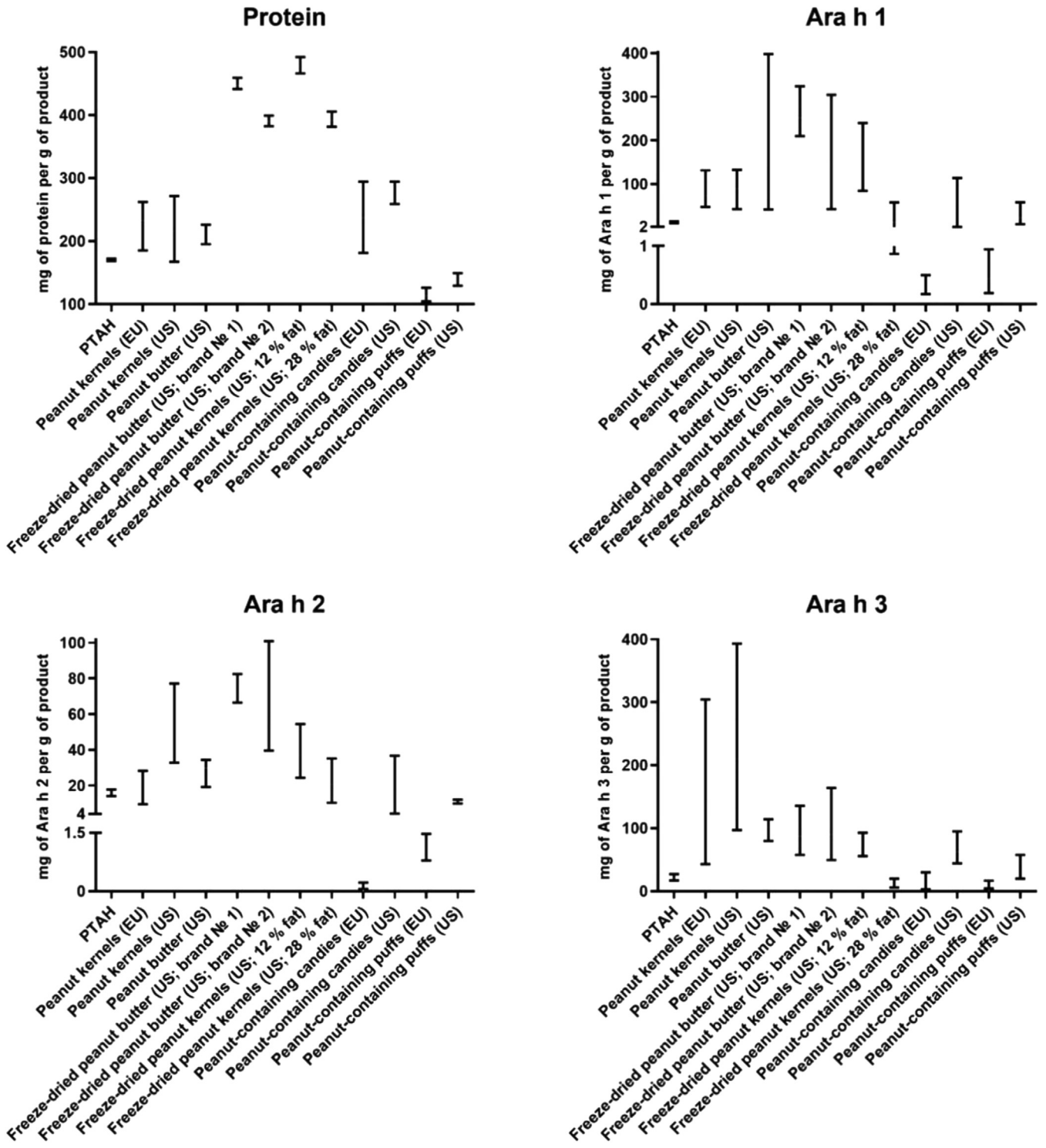

FIG 1. Concentrations of protein, Ara h 1, Ara h 2, and Ara h 3 in PTAH drug product and 11 peanut-containing food products. Horizontal bars represent the maximum and minimum values. *EU,* European Union; *US,* United States.

reactions resulting from accidental exposures in patients treated with these non–FDA-approved peanut products, especially when beginning a new lot or changing to a different peanut product. Although many small studies and noncontrolled studies have reported the benefits of off-the-shelf products for OIT, the lack of standardization of OIT regimens and the variability of peanut content in the products suggest that a more cautious approach is warranted. Peer-reviewed publications of well-designed studies are needed before widespread implementation. Given the substantial evidence indicating a high likelihood of unintended dose variation

TABLE I. Protein contents and concentrations of Ara h 1, Ara h 2, Ara h 3, Ara h 6, and Ara h 8 in PTAH drug product and 11 peanut-containing food products

Parameter		PTAH	Peanut kernels (EU)	Peanut kernels (US)	Peanut butter (US)	Freeze-dried peanut butter (US; brand 1)	Freeze-dried peanut butter (US; brand 2)	Freeze-dried peanut kernels (US; 12 % fat)	Freeze-dried peanut kernels (US; 28 % fat)	Peanut-containing candies (EU)	Peanut-containing candies (US)	Peanut-containing puffs (EU)	Peanut-containing puffs (US)
Protein content	Mean (mg/g)	170	233	216	217	447	390	478	391	237	275	113	140
	RSD*	1%	15%	17%	6%	2%	2%	2%	3%	18%	5%	7%	7%
	Max (mg/g)	172	262	271	226	459	399	492	405	294	294	126	149
	Min (mg/g)	168	185	167	195	441	382	466	381	181	259	104	129
	Max/min ratio	1.0	1.4	1.6	1.2	1.0	1.0	1.1	1.1	1.6	1.1	1.2	1.2
Content in Ara h 1	Mean (mg/g)	13	73	89	131	252	155	155	13	0.3	48	0.4	23
	RSD*	13%	46%	45%	115%	18%	63%	38%	196%	36%	101%	68%	88%
	Max (mg/g)	15	131	132	398	324	304	240	58	1	114	1	58
	Min (mg/g)	10	48	43	43	210	43	84	1	0.2	2	0.2	9
	Max/min ratio	1.4	2.8	3.1	9.3	1.5	7.1	2.8	67.5	2.9	50.3	4.9	6.8
Content in Ara h 2	Mean (mg/g)	15	18	47	30	73	57	38	21	0.1	14	1	11
	RSD*	11%	39%	40%	21%	9%	44%	32%	43%	54%	89%	22%	7%
	Max (mg/g)	18	28	77	34	83	101	54	35	0.2	37	1	12
	Min (mg/g)	14	9	33	19	66	40	24	10	0.1	4	1	10
	Max/min ratio	1.3	3.0	2.4	1.8	1.2	2.6	2.2	3.4	3.7	8.5	1.9	1.2
Content in Ara h 3	Mean (mg/g)	21	122	210	101	87	90	70	14	14	62	9	45
	RSD*	21%	87%	53%	14%	36%	51%	26%	37%	79%	33%	49%	35%
	Max (mg/g)	27	304	393	114	135	164	93	20	30	95	17	57
	Min (mg/g)	17	43	97	79	58	49	56	6	3	44	4	20
	Max/min ratio	1.6	7.1	4.0	1.4	2.4	3.3	1.7	3.4	10.4	2.2	4.0	2.9
Content in Ara h 6	Mean (mg/g)	5	9	24	13	27	24	17	10	0.1	7	1	5
	RSD*	11%	26%	64%	40%	21%	35%	17%	20%	129%	47%	21%	11%
	Max (mg/g)	6	12	50	20	34	35	19	12	0.2	11	2	5
	Min (mg/g)	4	6	7	7	18	14	13	7	0.01	3	1	4
	Max/min ratio	1.3	2.2	7.3	2.7	1.9	2.6	1.4	1.7	21.2	3.9	1.7	1.4
Content in Ara h 8	Mean (ng/g)	494	696	459	395	1011	924	776	249	127	365	108	361
	RSD*	4%	6%	13%	22%	9%	14%	20%	11%	13%	23%	14%	5%
	Max (mg/g)	509	759	528	534	1119	1101	913	279	148	472	133	393
	Min (mg/g)	461	639	377	307	892	755	511	223	104	252	97	342
	Max/min ratio	1.1	1.2	1.4	1.7	1.3	1.5	1.8	1.3	1.4	1.9	1.4	1.1

EU, European Union; *max*, maximum; *min*, minimum; *US*, United States.
*RSD characterizes lot-to-lot variability.

with unlicensed peanut sources and the theoretic risks associated with this variability, we believe that standardized products should be the preferred choice for OIT whenever available.

DISCLOSURE STATEMENT

Supported by Stallergenes Greer, the current licensee of PTAH.

Disclosure of potential conflict of interest: T. B. Casale has been a consultant for Thermostat Fisher and Stallergenes Greer and is on the scientific advisory board of Food Allergy Research and Education (FARE). C. A. Stone receives unrelated funding from the Agency for Healthcare Research and Quality (grant R01HS030234), the National Institute of Allergy and Infectious Diseases (grant U01AI181927), and the Vanderbilt Ingram Cancer Center/Chic Awareness program (pilot award for chemotherapy allergy research, and he is also a consultant for Stallergenes Greer. The aforesaid funders played no role in any aspect of this article. M. D. Chapman has a financial/ownership interest in InBio and is a consultant for Stallergenes Greer. S. A. Tilles is consultant for Stallergenes Greer and FARE. A.-M. Irani is a consultant for Stallergenes Greer. J. Sánchez-López, T. Batard, and L. Mascarell are employees of Stallergenes Greer.

We wish to thank Guillaume Sarrailhé, Mélanie Bilong, Sonia Luce, Delphine Baveux, Christine Caille, Céline Bianchi, Yonna Anaclet, Erika Petter, and Karine Jain for their excellent technical assistance. We also wish to thank Christel Dayang, Henri Chabre, and Christelle Péguillat for the technical supervision.

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https://doi.org/10.1016/j.jaci.2025.05.026