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SUPPORTING INFORMATION

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Real-life evaluation of tolerance to foods with precautionary allergen labeling in children with IgE-mediated food allergy

To the Editor,

Precautionary allergen labeling (PAL) statements on packaged food products such as "may contain" are confusing and are ignored by up to 40% of consumers with food allergies.[1,2] However, there is very little real-life data assessing the risk of introducing PAL foods in the community.[3,4] The aim of our study was to assess the real-life risk of reacting to foods with PAL in children with IgE-mediated food allergy regularly ingesting these foods.

Children with a physician-confirmed diagnosis of food allergy were recruited at the pediatric allergy unit of the Geneva University Hospitals between 2018 and 2021. Individuals and their caregivers were invited to fill out a survey on PAL (Table S1) during a regular clinical visit. They were eligible if they were 2–18 years of age, had a confirmed IgE-mediated allergy to at least one food (peanut, tree nuts, sesame, soy, wheat, egg, and milk), and were eating foods with PALs on a regular basis (see Online Supplementary file).

A total of 100 patients were included. Demographic characteristics of the 100 survey respondents are presented in Table 1. The median age at the time of survey was 6 years old. Peanut allergy was the most common diagnosis (58%) followed by cashew (52%) and hazelnut (42%). Most patients (76%) had multiple food allergies with a median number of three. The median age of the first food allergy diagnosis was 1.6 years and patients had been living for a median of 4.3 years with food allergy at the time of the survey. The median food specific IgE for each allergen is listed in Table S2. A total of 75 oral food challenges (OFCs) were performed in 60 patients at diagnosis. All OFCs were positive with a median reaction severity grade of 2 according to the scale by Sampson (range 1–4).[5] The median cumulative reactive dose (CRD) for all allergens combined was 430 mg of protein (Table S3 for CRD per allergen).

The main survey findings are presented in Table 2. The majority of children ate foods with PALs two to five times a week (57%), and

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TABLE 1 Patient Characteristics.

Number of patients	100
Female (%)	44
Median age at the time of the survey (range)	6 (1–17)
Atopic dermatitis (%, $n=99$)	64
Allergic rhinoconjunctivitis (%)	48
Asthma (%, $n=99$)	41
Food allergy diagnosis (%)	
Positive OFC (<1 year)	35
Clinical History (reaction <1 year) and positive SPT and/or positive sIgE	25
Clinical History (reaction >1 year ago) and/or positive OFC (>1 year) and sIgE above 95% PPV	56
Food Allergy (%)	100
Peanut	58
Cashew	52
Hazelnut	42
Pistachio	40
Walnut	35
Egg	21
Raw egg OFC	2
Baked egg OFC	7
Sesame	19
Almond	14
Milk	13
Raw milk OFC	2
Baked milk OFC	5
Macadamia Nut	12
Brazil nut	7
Pine Nut	7
Pecan Nut	5
Wheat	4
Soy	3
Patients with multiple food allergies	76
Median number of food allergies (range)	3 (1–10)
Median age at the first food allergy diagnosis (range)	1.58 (0.3–14)
Median sIgE in kU/L (range)	4.75 (0–100)
Median OFC cumulative reactive dose (mg of protein, range)	430 (15–9000)
Median OFC Sampson reaction severity grade[5] (range)	2 (1–4)

Abbreviations: OFC, oral food challenge; PPV, positive predictive value; SPT, skin prick test.

a large number every day (28%). Out of the 100 respondents, only 18 individuals (18%) had a previous reaction to foods with PALs. The majority of reactors (61%) had two to five previous reactions. Chocolates, cookies and cakes with PAL were the top three culprits, with chocolate being responsible for the most severe reaction in the

TABLE 2 Main survey results.

Eating habits with "may contain" foods (%)	
Less than 1×/week	6
1×/week	9
2–5×/week	57
Everyday	28
Foods eaten with PALs (%)	
Cookies	87
Chocolates	70
Cakes	58
Cereals	57
Breads	48
Bars	35
Pasta	18
Flour	13
Frozen dishes	12
Soups	5
Other	15
Preoccupied by labels with "may contain" (%)	
Not at all	35
A little bit to somewhat	47
Fairly to very	18
Previous reaction to foods with "may contain" (n, %)	18 (100)
Number of previous reactions	
1	4 (22.2)
2–5	11 (61.1)
6 or more	3 (16.7)
Most severe reaction	
Foods involved	
Chocolates	9 (50)
Cookies	2 (11.1)
Cakes	1 (5.6)
Chips	1 (5.6)
Pasta	1 (5.6)
Pesto	1 (5.6)
Unspecified	3 (16.7)
Type of reaction	
Urticaria	6 (33.3)
Oral pruritus	10 (55.6)
Skin angioedema	5 (27.7)
Abdominal cramping	2 (11.1)
Vomiting	4 (22.2)
Median Sampson reaction severity grade (range)[5]	1 (1–2)
Treatment received	
No treatment	5 (27.8)
Antihistamine	13 (72.2)
Epipen	0 (0)
ER visit	0 (0)

Abbreviation: PAL, precautionary allergen labeling.

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majority ($n=9$, 50%). Most reactions occurred within 10 min after two to five bites of food intake. The reactions were all mild with skin and/or digestive symptoms. The majority of the reactions were treated with second-generation antihistamines or required no treatment at all. None required emergency room visit or the use of epinephrine auto-injector.

The risk of reacting to foods with PAL was not influenced by gender, age, atopic background, and type of food allergy. The median sIgE was slightly higher in reactors (6.92 kU/L) compared to nonreactors (4.23 kU/L) but this was not statistically significant (NS). The OFC CRD was slightly lower in reactors (419.5 mg of protein) compared to nonreactors (535.5 mg of protein) (NS).

In this cohort of children with confirmed IgE-mediated food allergy, the majority did not report any reaction to foods with PAL (82%), and for those who did, the reactions were rare and mild.

Of interest, patients in this study had a relatively high median reactivity threshold close to the ED50 (population eliciting dose expected to trigger an allergic reaction in 50% of allergic subjects) or above for many allergens,[6] which might explain the high level of tolerance to these foods. One patient in five (18%) did however react to these foods at least on one occasion in the past, which seems a relatively high figure when compared to previous published reports,[3,4] although not directly comparable. There was no significant association between allergic reactions to PAL foods and reactivity threshold on OFC suggesting that heterogeneous particulate contamination might be involved and/or that cofactors might influence reactivity threshold in some circumstances.[7]

There is a growing interest in considering alternatives to strict allergen avoidance and encouraging an individualized management approach to PAL based on reactivity threshold, thus allowing ingestion of foods with PAL in some patients with food allergy.[8,9] One approach to risk stratification might involve performing a single-dose OFC as a decision point to allow PAL-containing foods.[9,10] However, determining the challenge dosage is challenging due to the significant protein content variation in PAL-containing foods and the heterogeneity of population eliciting doses by allergen.[6,11] This underscores the importance of standardizing PAL at both national and international levels.

The strengths of the study include a well-characterized cohort of patients followed at the pediatric allergy unit of the Geneva University Hospitals with confirmed IgE-mediated food allergy, a significant number of whom have undergone OFCs, and with regular exposure to foods with PAL. Limitations include recall bias which might have led to overestimation of self-reported reactions.[12] In addition, the population consisted predominantly of patients with nut/peanut/multiples food allergies which might be at higher risk of reacting to these foods. Finally, we cannot exclude that geographical variations in food allergen cross-contamination management practices by the food industry might lead to different reactivity profiles in other countries.

All in all, our study demonstrates a reassuring safety profile of PAL food ingestion in a real-world setting and supports the possible introduction of foods with PAL in certain patients with confirmed IgE-mediated food allergy and high reactivity thresholds. We were not able to isolate characteristics that increased the risk of reacting to these foods. Future larger prospective studies from different centers including heterogeneous food allergy profiles and reactivity thresholds are needed to better characterize the real-world consumers' risk when faced with these products and to better identify the patients that can introduce them safely.

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KEYWORDS

food allergy, oral food challenge, may contain traces, precautionary allergen labeling

AUTHOR CONTRIBUTIONS

François Graham contributed to the design of the study, recruitment of patients, the analysis of the results, the drafting of the manuscript and the critical revision of the manuscript. Avigael H. Benhamou contributed to the recruitment of patients, the analysis of the results, and the critical revision of the manuscript. Yan Jiao Liu contributed to the analysis of the results, drafting of the manuscript, and critical revision of the manuscript. Jean-Christoph Caubet contributed to the design of the study, recruitment of patients, the analysis of the results, and the critical revision of the manuscript. Philippe A. Eigenmann contributed to the design of the study, recruitment of patients, the analysis of the results, the drafting of the manuscript and the critical revision of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Authors have no conflicts of interest to declare pertaining to this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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