

Title: Can my child with IgE-mediated peanut allergy introduce foods labeled with “may contain traces”?

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Running Title: Attitude towards foods with “*may contain traces*”

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Abstract: Peanut IgE-mediated food allergy is one of the most common food allergies in children with a prevalence that has increased in the past decades in westernized countries. Peanut allergies can trigger severe reactions and usually persist over time. Peanut-allergic children and their families are often confronted to processed foods with precautionary allergen labeling (PAL) such as “may contain traces of peanuts”, which are frequently used by the food industry. Patients are generally confused as to whether eating such foods entails a risk of allergic reaction, which can ultimately lead to dietary restrictions and decreased quality of life. Thus, guidance towards eviction of foods with PALs such as “may contain traces of peanuts” is a recurring problem that peanut-allergic patients address during pediatric allergy consultations with varying attitudes among allergists. Many studies have evaluated peanut contamination in foods with PALs, with generally less than 10% of foods containing detectable levels of peanuts, albeit heterogeneous amounts, with in rare occasions levels that could trigger allergic reactions in certain patients. The risk of reacting to foods with traces varies significantly with threshold, with patients with the lowest reaction thresholds at highest risk, and a dramatic reduction of risk as threshold increases. Thus, risk stratification based on individual reaction threshold may help stratify patients' risk of reacting to foods with PAL. In clinical practice, a single dose 30 mg peanut protein oral food challenge may be an option to

stratify peanut-allergic patients' risk when introducing foods with PAL, as illustrated by 3 clinical cases.

Keywords: May contain traces, precautionary allergen labeling, food allergy, peanut allergy, oral food challenge, single dose oral food challenge, quality of life, threshold, minimal eliciting dose, quantitative-risk assessment

1- Introduction

IgE-mediated peanut allergy in children has increased in recent decades, with some countries having a prevalence as high as 3% of the population (1). Management of IgE-mediated peanut allergy generally involves strict avoidance, with treatment of accidental reactions. Quality of life (QOL) is impaired in patients with peanut allergy due to dietary restrictions and hypervigilance (2), especially with foods that have not been introduced yet and during social activities. In addition, peanut-allergic children and their families are confronted to foods with precautionary allergen labels (PAL) on packaged products such as “may contain traces of peanuts ” or “may contain peanuts”, which are confusing, and can increase anxiety of parents and children (3, 4). These PALs are used inconsistently by the food industry and do not always reflect actual risk to the allergic patient (4-6). To further complicate matters, PAL laws vary from one country to another. For instance, in Switzerland allergens not added voluntarily and that exceed 1g/kg must be declared, whereas some other countries have no legislation at all concerning PAL (7). Thus, a common question that allergists are confronted with is whether the introduction of foods with “may contain traces” labeling is safe for a given patient, and if not, how strict avoidance needs to be. Anecdotally, this approach is variable among countries, with some allergists authorizing the introduction of all foods with PAL, and others restricting all contact with foods with PAL. Another approach is to offer tailored advice and allow consumption of non-snack foods with PAL in some peanut-allergic patients after discussion with the patient and his family and based on multiple personal factors (history of reactivity to trace levels of peanut, reaction severity, other medical conditions, willingness to always carry adrenaline...)(8). Unsurprisingly, it was shown that up to 40% of children with food allergies consume foods with PAL, irrespective of advice given by physicians (9). Nevertheless, the remaining proportion (60%) of patients avoiding all foods with PAL remains significant. This can affect choices of consumed foods and likely result in impaired QOL. In our practice, the majority of patients strictly avoiding the "may contain" foods report that this avoidance diet causes important disruption in daily life, in

particular at the school restaurant where the patients often have to bring their own meals. Thus, one of the main requests of the parents is "does my child really need to avoid "may contain" foods?", and "what is the risk of eating them?". Although future quantitative-risk assessment (QRA) approaches by the food industry based on populational eliciting doses may help eliminate unnecessary PAL and reduce risk for patients (4), guidelines on personalized recommendations for patients are currently inexistent, leaving patients with no real solution in front of these ubiquitous foods. This Rostrum will focus on patients with peanut allergies and consumption of prepacked foods with PAL. The discussion is not applicable to other allergens and non-prepacked foods.

2- Do foods with peanut precautionary labeling actually contain traces of peanuts?

While most countries require mandatory labeling of major allergens which are part of food ingredients such as peanuts, tree nuts, milk, eggs, crustacean shellfish, fish, soybeans, and cereal sources of gluten based on Codex Alimentarius (10), precautionary allergen labeling is generally voluntary and used inconsistently across the food industry (11). Many food manufacturers use PAL only when there is a real risk of inducing an allergic reaction (proper risk assessment) based on good manufacturing practices (GMP). Unfortunately, some manufacturers use PAL when there is an unknown risk of allergic reaction, or when the risk is low or absent but decision to use PAL remains due to risk aversion(11). On the other hand, some small or medium business do not use PAL when required because of lack of awareness, which can be a major issue as they contribute to supplying larger companies and involve a large proportion of food supply in many countries (11). In addition, PALs are now used for non-prepacked foods (ie. from restaurants/caterers/delicatessens ...) since December 2014 in Europe (EC Regulation No. 1169/2011) (8).

Many studies have measured the doses of peanut traces in foods with PAL, albeit a very small number of samples compared to the number of processed foods produced every day. Risk of residues varies with types of foods consumed, with high-risk products such as chocolates, cookies, and bars having a higher risk of contamination, although high-risk foods without PAL are also at risk of having detectable residues (10). All in all, only a small proportion of foods with PAL have been found contaminated with peanut traces (generally less than 10%), with quantities varying from 0.9 to 26,000 ppm of whole peanut (ie. approximately 0.0225 to 650 mg of peanut protein per 100g of food) (12). When looking at these studies, it is important to look at the median residues found, although not always clearly

expressed, since there is often an outlier with high residues that does not represent the distribution of residues in these products. For example, 26,000 ppm was only found in 1 study in 1 sample (13). In this same study, the median ppm whole peanut in positive sampled packaged nutrition bars with advisory labels was 28.4 ppm (13), which represents 0.71 mg peanut protein per 100 g. This level might cause symptoms in patients with very low reaction thresholds representing only a minority of peanut-allergic patients (12). Other similar studies found median amounts of peanut protein per serving between 0.07 (14) and 0.46 mg (15). Overall, these data suggest low-grade contamination in a minority of samples analyzed.

Although seemingly reassuring, these data need to be interpreted cautiously as heterogeneous distribution of contaminating allergen residues in products can influence these results (10). Apart from having completely allergen-free production lines with full HACCP-type monitoring, it is impossible to reliably assess for allergen contamination with nut particulates in solid foods, since any contaminating allergen may be non-uniformly dispersed in the analysed foods (11). This is the main reason why structures such as Voluntary Incidental Trace Allergen Labelling (VITAL 2.0) (16) have focussed on initial risk assessment rather than monitoring of food products for allergen contamination to determine which products required PAL.

3- To what quantity of peanut do peanut-allergic patients react?

Several studies have been undertaken to determine eliciting doses (EDs) in the peanut-allergic population (ie. minimal dose which can trigger an allergic reaction) for risk-assessment purposes in front of foods with PAL (17-19). Population thresholds that are predicted to trigger a reaction in 1%, 5%, 10% and 50% of allergic subjects (ED1, ED05, ED10, ED50 respectively) have been described (17, 20). Estimating population EDs is complex, since these can vary with the population studied (children vs adults) and depend on interpretation of oral food challenge (OFC), as subjective and objective symptoms can occur at different EDs (2-6 fold higher EDs for objective compared to subjective symptoms) (21). In addition, most of these EDs data have been obtained from studies in tertiary centers often selecting the most severe allergies, and real life EDs are likely higher. Depending on studies, ED01 vary from 0.15 (21) to 0.2 (16) mg peanut protein, ED05 from 1.56 to 5.08 mg peanut protein (16, 18, 21, 22), ED10 from 2.8 to 87 mg peanut protein (18, 21-24), and ED50 from 29.9 to 300 mg peanut protein (18, 19, 21, 25). For quantitative risk assessment, there is a need to have a confidence interval at the lower ED margin (ie. ED01 or ED05) in order to

protect most peanut allergic patients (“tolerable level of risk”), taking into account that a zero risk scenario is not practicable or realistic (26).

4- Do patients react when consuming foods with PAL in the community?

Data on reactions to foods with PAL in the community are sparse. Recently, Zurzolo et al performed a large survey in Australia of which 198 members of the Australasia Society of Clinical Immunology and Allergy (including physicians, dieticians, nurse practitioners) responded over a period of 9 months (27). They described 14 reports of anaphylaxis to presumed allergen contamination in packaged foods. Another prospective study from Denmark followed accidental reactions over a period of 1 year in adults with IgE-mediated food allergy (28). In this study 5/157 (3.2%) had confirmed reactions to foods with “may contain traces”, with other accidental reactions caused by foods without precautionary allergen labeling or with foods having the principal allergen listed in the ingredients. Overall, these studies suggest that only a small percentage of patients report reactions to foods with PAL.

5- Can we use individual threshold to stratify risk of reacting to foods with PAL?

While populational thresholds can help identify peanut-allergic patients with the lowest reaction thresholds and can be used to guide legislation for more comprehensive and standardized PAL, they do not help to quantify the risk of a reaction for a given peanut-allergic individual when consuming products with PAL. Indeed, many patients have a high reaction threshold during OFC: up to 50% of children with peanut allergy react at a cumulative dose of more than 300 mg peanut protein (25).

Thus, another approach is to perform quantitative risk assessment based on individual threshold (29). Baumert et al. estimated that a threshold value of 30 mg peanut protein would cause symptoms in 0.9 to 4.5% of eating occasions when consuming high-risk PAL products. This model is conservative and assumes that all PAL labelled foods contain peanut residues, when they are only found in less than 10% of sampled products, and the real risk is likely significantly lower at this threshold.

Overall, the risk of reacting to foods with traces varies significantly with threshold, with patients with the lowest reaction thresholds (ie below the ED05 or ED10) at highest risk, with a dramatic reduction of risk as threshold increases (29). Thus, risk stratification based on reaction threshold may help stratify patients’ risk of reacting to foods with PAL.

6- How can we assess individual threshold?

Determination of individual threshold is complex and affected by intrinsic and extrinsic factors (12, 30). In addition, no *in-vitro* or *in-vivo* test (skin test, specific IgE, basophil activation tests) can reliably predict reaction thresholds (31, 32). Thus, the gold standard for threshold determination is the OFC, although no single approach has been universally accepted. Most clinicians perform graded OFCs mainly for security purposes with intervals varying from 15 to 30 minutes between doses (33-35). The PRACTALL guidelines suggest performing graded OFCs starting from 1 mg of protein up to a total of 3000 mg of protein at least every 15-20 minutes (35). Although useful for a dichotomous answer (reaction or no reaction), this protocol may overestimate the reaction threshold by inducing temporary desensitization to the ingested allergen (36) and may not reflect an accurate representation of trace exposure in the community, which is in the form of a single dose of allergen. In addition, it is difficult to know during graded OFC if the patient is reacting to the most recent dose or to the previous dose. This is illustrated by a study by Blumchen et al. who used a modified OFC protocol with doses given every 2 hours (37). The median latency of clinical reaction was 55 minutes, which is much longer than the dosing time intervals of 15-20 minutes suggested in the PRACTALL consensus (35).

Single dose challenges, on the other hand, are easier to perform (32), less time-consuming, and more representative of actual ingestion of allergens. Another advantage is their easier implementation in less expert centers. However, they do not offer a precise reaction threshold, since this threshold can be either above or below the ingested quantity. They do on the other hand give an approximate estimation of severity of reaction after a given dose of allergen.

Although the previously mentioned OFCs can give an approximation of reaction threshold on an individual day, reproducibility of eliciting doses may be influenced by a number of host-related and allergen-related factors (30, 38-40). In particular, cofactors such as exercise or sleep deprivation (41) can play a role in influencing threshold of reaction. One option to evaluate the variability of individual eliciting doses would be to perform a 2nd food challenge in the presence of cofactors such as exercise or NSAIDs (42); however, this would be resource/time consuming, and difficult to implement in routine clinical practice.

7- And in practice? Three different representative cases:

The limitations of PAL discussed above are facts to which our patients are daily exposed, despite the continuous and acknowledged efforts of the industry to improve the accuracy of PAL. Our aim here is to improve the quality of care from a patients' perspective, as all patients are not equal when confronted to PAL.

One option to evaluate safety of introducing foods with PAL would be to perform a single dose challenge (single-blind or double-blind) with a quantity of protein representing the upper limit of peanut contamination found in foods with PAL (ie, approximately 30mg peanut protein (14, 43, 44), with in very rare instances sporadic samples with slightly higher values (13, 15)). The result of this single dose OFC could be used to assess individual risk of introducing foods with PAL and would be less resource intensive than regular graded OFCs (ie. for non-tertiary centers). We have used this approach for certain peanut-allergic patients consulting in pediatric allergy at the University Hospitals of Geneva, as illustrated by the 3 following clinical cases.

We acknowledge that such an approach may not be appropriate for all patients avoiding foods with PAL and needs to be adapted depending on patients' preferences and needs via shared decision making. Patients with a very high-risk aversion will continue to avoid all foods with traces. Other patients will introduce traces without even consulting physicians. Finally, some patients will want to have guidance towards introduction of these foods, and the proposed single dose OFC may help better stratify the risk these patients will be taking when introducing these foods.

7.1 First clinical scenario: no reaction at 30mg peanut protein on OFC

The first clinical scenario is of a 10-year-old boy with a history of peanut, egg, and milk allergy. The patient and his parents were extremely anxious of having an allergic reaction to foods with "may contain traces" and strictly avoided these foods. The patient and his parents were not interested in peanut oral immunotherapy (OIT) and were interested in knowing if foods with "may contain traces" could be introduced. Peanut specific IgE was 2.72 kU/L and Ara h 2 0.7 kU/L. We offered a 30 mg PP single blind OFC, with no clinical reaction at this dose. We proposed to pursue peanut OFC to confirm allergy, but the patient and parents both refused. They were authorized foods with may contain traces at home and were extremely satisfied with this outcome. In this scenario, pursuing the OFC would have been ideal to confirm the presence of allergy and threshold of reaction, although ara h 2 levels were above

the 95% positive predictive value (PPV) (45). We followed-up 3 months later and the patient had been able to introduce a variety of foods with no reaction to products with PAL.

Although the proposed stratification with a 30mg PP OFC is meant to guide patients' risk when eating with PAL, all patients with IgE-mediated peanut allergy have a theoretical risk of reacting to foods with PAL, including patients who do not react at 30mg PP OFC.

Nevertheless, the risk for these patients is quite low; a conservative estimate is that peanut-allergic individuals with 100 mg OFC threshold (ie. the next dose after 30 mg when following PRACTALL OFC guidelines (35)) would possibly react between 0.1 and 1.4% of eating occasions, based on a 100% of foods with PAL containing traces (actual numbers are generally below 10%) (29). Thus, these patients with no reaction at 30mg of peanut protein have a theoretical very low risk of reacting and we allow introduction of foods with PAL in this group of patients, albeit explaining this theoretical small risk. We would still encourage carrying adrenaline kits in these patients since they are still considered allergic to peanuts and may have a severe reaction after accidental exposure to a larger amount of peanut protein in the community (at a restaurant for example).

7.2 Second clinical scenario: mild reaction at 30mg peanut protein OFC

The second case is of a 15-year-old boy with IgE-mediated peanut allergy since he was a child. The patient had been avoiding all foods with « may contain traces of peanuts and nuts ». He had not had an accidental reaction to peanuts since the age of 9 and was interested in knowing whether foods with precautionary allergen labeling could be introduced. Specific IgE to peanut and Ara h 2 were over 100 kU/L (above the 95% PPV). The child and his parents felt that introducing foods with “may contain traces” could greatly improve their quality of lives and were very worried about introducing these foods at home. We thus proposed a 30 mg PP single blind OFC. He initially experienced no symptoms to the placebo muffin, and then went on to experienced isolated oral pruritus that lasted 15 minutes with the peanut-containing muffin. In this context, we introduced 3 “high risk” foods with PAL under clinical supervision (chocolate, biscuit, cereals), which were all tolerated without symptoms. We then allowed the introduction of foods with PAL at home. The patient was advised to contact us in case of reaction to these foods and was reminded to continue strict avoidance of foods with peanuts listed as ingredients on labels, and to continue carrying his epinephrine autoinjector, as previously required. He was able to introduce 20-30 different types of foods without any significant clinical reaction at home when we saw him at follow-up after 3

months. The patient and his family were greatly appreciative and expressed an improvement in QOL.

We recommend being more cautious with patients who have a mild reaction at 30mg peanut protein OFC, since there is slightly higher risk in these patients. We only allow introduction of foods with PAL at home after hospital supervised introduction of high-risk products with PAL, and follow-up 3 months later to assess tolerance of these foods at home. In addition, we encourage avoidance of foods with PAL in the presence of cofactors in these patients, since predictors of severity and threshold of reaction in the community are complex and not well characterized (30, 38, 39), as discussed earlier in section 6. Furthermore, one cannot guarantee that a products eaten on numerous occasions will not contain allergenic residues on a following occasion (46). Thus, this may leave patients in a scenario where they feel comfortable eating a product and could leave them at risk of an unexpected reaction after eating a product tolerated many times in the past. Another preoccupation is whether allowing foods with PAL might encourage increased risk taking in restaurants and other areas where traces are present. We always caution patients to continue avoiding restaurants where trace exposure is possible, and to carry their portable epinephrine injectors as detailed in their action plans. An ongoing study by our center will help to better define whether such an approach is risky and whether patients' QOL is improved (NCT03680066).

7.3 Third clinical case: moderate to severe reaction at 30mg protein OFC

The third clinical case is of a 10-year-old boy with IgE-mediated peanut allergy since the age of 2. Specific IgE to peanut and Ara h 2 were respectively 84.60 kU/L and 67.60 kU/L. The parents had many limitations in their choices of foods at the supermarket and were interested in introducing foods with “may contain traces”, as their child would love to be able to eat deserts and chocolates. We performed a 30 mg single blind peanut protein OFC, and the patient developed mild oral pruritus, severe abdominal pain (9/10), and vomiting. He was treated with intramuscular adrenaline and oral cetirizine with a resolution of symptoms. Since his symptoms were moderate to severe at this low dose of peanut protein, the patient was advised to continue avoiding foods with traces, as they potentially could present a significant risk for this particular patient.

We consider a patient with a moderate or severe reaction on the single dose 30 mg protein OFC as a high-risk patient who could potentially present a severe reaction in the community when consuming foods with PAL. In this scenario, we would encourage strict avoidance of

all foods with PAL. We would also discuss the benefit of performing OIT to increase patient's threshold, which could reduce the risk of accidental reactions to traces (27).

8- Conclusions:

Avoidance of foods with “may contain traces” is a recurring problem that peanut-allergic patients address during pediatric allergy consultations with no definite answer. Patients often express their frustration towards PAL and limited options in stores because of the extensive number of products with PAL. Introduction of foods with PAL not only enables the introduction of a larger diversity of foods but may also increase the QOL of patients with peanut allergy and their families. However, introducing these foods may be risky, especially in peanut-allergic patients with low reaction thresholds. Thus, in clinical practice, a single dose 30 mg PP OFC may be an option to stratify these patients' individual risk of reacting to foods with PAL in the community as illustrated in the previous clinical cases.

A standardised QRA approach based on VITAL (16) thresholds is being established so that only products likely to contain unintentional allergen residues above a predefined threshold (ie ED01 or ED05) and likely to cause a reaction have PAL statements (4). These measures will hopefully reduce the number of products with unjustified PAL statements and ultimately facilitate decision making when confronted with these foods. However, a long path is ahead before these QRA methods will come into place, due to the complexity of wide-scale implementation of such measures. Taking into account the patient's perspective, individual risk stratification with a single dose 30 mg peanut protein OFC may be a current option to better guide patients when confronted with the dilemma of introducing these ubiquitous foods.

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