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CHAPTER 6

Food Allergen Thresholds of Reactivity*

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KEY CONCEPTS

- Threshold doses of food allergens do exist below which patients will not react adversely to residues of an allergenic food.
- Threshold doses vary considerably from one patient to another.
- Clinical determination of threshold doses is best done through double-blind, placebo-controlled food challenges.
- Knowledge of individual threshold doses can provide guidance to patients in the successful implementation of avoidance diets.

Until more innovative therapies are developed and implemented, food-allergic individuals must adhere to specific food avoidance diets. In general terms, allergists advise food-allergic patients to avoid completely the specific allergenic food(s) and all ingredients made from those food(s). The presumption is made that the threshold dose for the offending food is zero and thus complete avoidance is a necessity. From a practical perspective, this advice is probably prudent. Food-allergic individuals can react adversely to exposure to small quantities of the offending food [1,2], but it is now well documented that food-allergic individuals have threshold doses below which they will not experience adverse reactions [3,4]. Ultimately, that information could be helpful to allergic individuals, their physicians, the food industry, and governmental regulatory agencies in protecting the health of these consumers. However, the determination of individual threshold doses is not yet a common clinical procedure and no consensus exists on the establishment of regulatory threshold doses below which the vast majority of a population of patients allergic to a specific food, for example peanut, would not be expected to react.

Definition of threshold

A good discussion about the usefulness of threshold presupposes that there is a universally held definition for the term threshold. In much of the existing clinical literature, the threshold dose is operationally defined as the lowest dose capable of eliciting an allergic reaction. From the toxicology

and risk assessment perspective, this dose would be known as the lowest observed adverse effect level (LOAEL) or the minimal eliciting dose (MED) [3]. However, from a risk assessment perspective, the threshold dose should actually be defined as the highest amount of the allergenic food which will not cause a reaction in individuals allergic to that food. This dose would be known as the no observed adverse effect level (NOAEL). Unfortunately, in much of the clinical literature on dose–response relationships for allergenic foods, the NOAEL is not clearly reported.

Clearly, NOAELs and LOAELs can be defined on either an individual basis or a population basis. For an individual, the NOAEL or LOAEL can be experimentally determined by challenge trials conducted in a clinical setting on a particular day. Individual NOAELs or LOAELs might vary from one day to another or from one season to another based on many factors that are not completely understood. Few studies have been done comparing individual NOAELs or LOAELs from one occasion to another, although it is well described that pediatric patients [5] and patients undergoing successful immunotherapy [6] can become more tolerant of an allergenic food. Certainly, considerable variation occurs in the NOAELs and LOAELs between individuals with a given food allergy. Individual NOAELs for peanut, for example, in controlled clinical challenges can range from low milligram levels to perhaps 10 g [7].

The population threshold can be defined as the largest amount of the allergenic food which will not cause a reaction

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when tested experimentally in a defined population of allergic individuals. Of course, this definition presumes that a representative population can be identified and tested experimentally that would include some of the most highly sensitive (as defined by dose) individuals. Clinically that can be difficult, especially if some patients, such as those with histories of severe reactions, are excluded from the clinical threshold trial. The derivation of the population threshold can also be approached through modeling of the dose–response relationship [8]. In this approach, the individual thresholds of ideally a large number of patients are plotted and examined statistically. In this case, the threshold is defined as the amount of the allergenic food which will not cause a reaction in a specified proportion of an allergic population. These different definitions imply the use of different approaches to the determination of thresholds that would have different uses in advising patients, labeling of foods, and regulating the food industry.

Thresholds for sensitization versus elicitation

Allergic responses occur in two phases: sensitization and elicitation. Thresholds may apply to both phases [8]. In the sensitization phase, the susceptible individual develops allergen-specific IgE antibodies in response to allergen exposure. Because allergic reactions have not yet occurred, the level of exposure to the allergenic food can be quite high, for example feeding of milk-based formula to an infant. However, clinical experience suggests, but does not prove, that some infants are sensitized by exposure to much lower doses of the allergenic foods via breast milk where the level of the allergens is presumably restricted to the small amounts that can transfer from the mother's digestive tract to the breast milk [9]. Cutaneous exposure to food allergens has been implicated in sensitization in retrospective case control series [10] and animal studies have confirmed that this is possible, especially through inflamed skin [11,12]. Very little information is known about threshold doses for sensitization, and gathering clinical evidence about thresholds for sensitization is likely unethical.

Therefore, this chapter will be devoted to a discussion of the threshold dose for elicitation. The MED is the lowest amount of the allergenic food needed to elicit an allergic reaction in a previously sensitized individual. These food-allergic individuals are the ones who implement specific avoidance diets and must be reasonably protected by food industry practices and labeling standards.

Clinical determination of individual threshold doses

Double-blind, placebo-controlled food challenge (DBPCFC) remains the gold standard for diagnosis of food allergy

[9,13]. The inclusion of extremely low doses of allergenic foods in challenges has been common in research practice for more than a decade [14]. Starting with lower doses means a longer challenge, as challenges must continue until the equivalent of a reasonable serving of the food has been consumed. While existing clinical data are somewhat limited, no correlation has yet been found between patients who react on challenge to very low doses and patients with histories of severe reactions. Indeed, severe reactions to the lowest doses used during the challenge have not been reported in any of the most cited studies and inclusion of low doses, for example 1 mg of peanut protein, is becoming the norm. It appears therefore that the inclusion of very low doses in DBPCFCs has further increased the safety of food challenges for research and clinical interests.

DBPCFCs that include low doses are now commonplace and most adhere to consensus protocols developed with input from stakeholders from the medical, industrial, and regulatory communities [15]. These challenges proceed in exactly the same fashion as “normal” food challenges. A major consideration has been how to set criteria for a definitive result. Subjective symptoms such as non-cooperation (in children particularly), abdominal pain, vomiting, or itch are easily elicited but are then difficult to quantify. Thresholds for subjective symptoms appear to be lower than for objective symptoms [16]. Comparison of apparently similar patients in similar or identical studies in different countries would be difficult if criteria for stopping a challenge were not standardized. It has been agreed that most low-dose challenges, especially in adults, should continue until objective signs are elicited, such as urticaria or angioedema. Subjective symptoms should be carefully recorded and more significant subjective symptoms such as abdominal pain in infants and children, in particular, are frequently considered as an adequate basis to stop the challenge trial [15]. However, as with other diagnostic food challenges, low-dose challenges should be stopped before more significant signs are elicited, such as wheeze. Put simply, low-dose challenge studies add up to three or four extra doses at the start of the challenge, but after the low doses have been safely consumed, there is nothing more complex about a low-dose challenge than there is for any other diagnostic food challenge.

There will always be concerns that volunteers for research studies are self-selected and that there are likely to be more sensitive subjects who do not wish to volunteer. Furthermore subjects who agree to undergo a challenge, whether clinically motivated or for research studies, must be in optimal health at the time of challenge, so the effects of asthma, reactivity to pollen, or use of medications such as ACE inhibitors are eliminated from the challenge in a way that they cannot be eliminated from exposures to allergens in the community [17]. Airway stability must be assessed before challenge by assessment of peak expiratory flow rate, FEV1 measurement, or formal spirometry. Regular medications that may affect

elicitation of an allergic reaction during challenge, such as antihistamines, must be stopped appropriately before challenge [13,15].

The severity of previous reactions by history was not an exclusion criterion for the first threshold study of 14 peanut-allergic patients [14] and published data now exist on more than 70 low-dose peanut challenges in subjects including “severe reactors” [14,18,19]. Flinterman [16] reported low-dose challenges in a group of children with a spectrum of clinical reactivity so it appears, therefore, that within the constraints of research-motivated challenges in volunteers, both adult and children, that a spectrum of clinical reactivity has been fully represented in low-dose challenges to date.

The use of standardized protocols is critical for direct comparison of challenge studies, as the outcome of challenges can be affected by considerations such as use of different vehicles for challenges [20] or different types of allergen, for example pasteurized egg powder versus cooked egg, defatted peanut flour versus roasted peanut, etc. [3].

Repeated food challenge is often necessary in children to ascertain persistence or resolution of food allergy. Clinical experience in pediatric practice suggests that increasing amounts of allergen can be tolerated as oral tolerance is achieved, suggesting a change in individual threshold doses, but this has not been formally evaluated. Changes in thresholds over time have not been extensively investigated, with isolated reports suggesting there is no substantial change in adults [14,21].

Clinical correlates of thresholds of reactivity

Allergen-specific IgE levels in serum and skin prick test wheal size are now widely used in clinical practice to assess the progress of oral tolerance acquisition in pediatric patients and to determine appropriate times for confirmatory challenge trials [22,23]. Furthermore, a Dutch study [24] reported that nine subjects with the lowest eliciting dose of peanut (0.1–1.0 mg peanut flour) had a higher median peanut-specific IgE value (44 kU_A/l) than three subjects with a higher threshold (>10 mg, peanut-specific IgE values 4.7 kU_A/l, $p = 0.018$). Thus, some correlation seems to exist between the levels of allergen-specific IgE levels in serum and individual threshold doses. However, it has not been possible to strongly correlate serum allergen-specific IgE levels or skin prick test wheal sizes with the severity of both reported reactions, and more importantly, of future exposures, possibly because many other factors are in play in community exposures [17]. Studies designed to specifically examine low-dose reactivity, however, have begun to alter this perception. A British study has shown a moderate inverse correlation between peanut-specific IgE levels and challenge-induced reaction score, which is stronger in adults than in children [17]. Wensing *et al.* [25] reported that subjects who reported moderate to severe reac-

tions during exposures to peanut in the community reacted (with mainly subjective symptoms) to significantly lower doses of peanut during low-dose DBPCFC than did subjects whose previous reactions had been mild ($p = 0.027$). In contrast, Hourihane *et al.* [18] found little correlation between “community” and “challenge” severity when an estimate of the dose of allergen was considered in the assessment of reaction severity. It appears possible that the inclusion of very low doses in challenges will improve the information that can be gathered from a challenge, and that the use of allergen-specific IgE levels could be developed for the prediction of the severity of reactions in challenges with peanut. This association remains to be demonstrated for other food allergens, and it is possible that the significance of allergen-specific IgE levels will remain confined to interpretation of low-dose challenge studies, rather than replacing them.

Minimal eliciting doses for specific foods

Oral challenges, often DBPCFCs, are often conducted as part of the clinical diagnostic procedure for patients suspected to have food allergy [9]. In the recommended clinical procedure, the initial dose for diagnostic challenges is described as less than that estimated by the patient to be required to produce symptoms [9]. Thus, considerable physician discretion and experience is involved in the selection of the initial dose in diagnostic DBPCFC. In routine clinical practice, challenge doses often start at 500 mg of the specific food [26], although lower initial doses are occasionally used when circumstances warrant. Sicherer *et al.* [26], in reporting on diagnostic DBPCFC experiences in 196 patients with 513 positive challenges, indicated that a large percentage of patients, ranging from 17% for fish to 55% for milk, reacted to the initial dose of the DBPCFC. While this approach is quite useful from a diagnostic perspective in clearly establishing the role of the specific food in the allergic reaction, it does not establish the individual NOAEL in patients reacting to the initial dose because doses well below 500 mg could provoke reactions in such patients. In fact, 11% of patients experienced severe reactions to the initial dose [26] perhaps suggesting that the initial dose was considerably higher than the patient’s MED. Other clinical investigators have similarly reported severe reactions occurring to the initial dose in a diagnostic DBPCFC [27].

In their diagnostic experiences with DBPCFC, Sicherer *et al.* [26] reported that half or more of allergic individuals had MEDs of 600 mg or more, ranging up to 8 g [26]. Similar results were reported by Morisset *et al.* [7] in sharing clinical experiences with large numbers of patients involved in diagnostic DBPCFC and in results from several immunotherapy trials for peanut allergy [6,28,29]. Thus, the majority of food-allergic individuals are likely to experience reactions only when exposed to food that has been rather seriously contaminated or mislabeled.

Very importantly, some exceptionally sensitive patients exist. Individual patients with MEDs of 1 mg have been described for peanut and egg, with even occasional lower MEDs for milk in some infants [3]. The percentage of patients with individual MEDs that are well below (<100 mg) the typical initial dose used in diagnostic DBPCFC is unknown. The identification of such patients may be quite important, as these are predicted to be the individuals who would be at greatest risk from exposure to foods contaminated with trace levels of the offending food.

Clinical trials using low-dose challenges have been conducted on peanut [6,7,14,16,20,24,25,28–32], milk [7,32–35], egg [7,32,34,36], and hazelnut [37–39] for multiple purposes including diagnosis, the determination of thresholds, or the evaluation of various therapeutic treatments. Sufficient number of patients have been included in these various trials to perhaps allow the determination of a population-based threshold dose, although various factors, as discussed below, complicate the interpretation of the collective data [3]. Similar trials have been conducted on smaller groups of patients for soybeans [35,40], mustard [41,42], fish [43,44], and sesame seed [7], but the groups are too small to make population-based estimates. Table 6.1 provides a list of published studies where low-dose challenge studies have been conducted on one or more patients with peanut, egg, milk, hazelnut, soybean, fish, mustard, shrimp, or sesame seed allergy. From Table 6.1, individual MEDs appear to be quite variable, ranging from approximately 1 mg to as much as several grams.

The interpretation of these data to determine population-based thresholds is complicated by numerous factors. The use of a study population that is representative of the entire cross-section of individuals allergic to a particular food should be an essential feature in the determination of population-based thresholds. The compilations of diagnostic challenge experiences indicate that the majority of food-allergic patients have individual threshold doses above the typical 500 mg initial dose used in diagnostic challenges [7,26,27]. An examination of the studies reviewed in Table 6.1 indicates that low-dose challenge trials seem to include a preponderance of patients who have lower individual threshold doses. This observation is not surprising since the use of low doses in diagnostic challenges is typically predicated on the patient's historical accounts of reactions to ingestion of small amounts [9,26], but suggests that these individuals may not be representative of the entire population allergic to a particular food.

Other factors also lead to uncertainty in the establishment of population-based threshold using existing published data. In many cases, the LOAELs are reported but NOAELs are not or must be inferred. The doses are reported as discrete doses in some cases and cumulative doses in others. More importantly, the challenge materials are not consistent and need to be normalized to some factors such as protein, but the protein levels in the challenge materials are not given. For example, peanuts are approximately 25% protein while peanut flour

Table 6.1 Published studies on low-dose challenges

Reference	Number of patients	Range of MEDs ¹
<i>Peanut</i>		
May (1976) [32]	8	0.200–8.0
Atkins <i>et al.</i> (1985) [45]	3	0.500–50
Moneret-Vautrin <i>et al.</i> (1995) [34]	2	0.10–10
Oppenheimer <i>et al.</i> (1992) [28]	11	0.030–8.0
Hourihane <i>et al.</i> (1997) [14]	8	0.002–0.050
Nelson <i>et al.</i> (1997) [29]	12	0.016–2.8
Moneret-Vautrin <i>et al.</i> (1998) [31]	9	0.200–0.965
Wensing <i>et al.</i> (2002) [25]	26	0.0001–1.0 ²
Morisset <i>et al.</i> (2003) [7]	103	0.005–>7.11
Leung <i>et al.</i> (2003) [6]	23	0.001–2.0
Grimshaw <i>et al.</i> (2003) [20]	4	0.006–0.936
Lewis <i>et al.</i> (2005) [30]	40	0.001–3.936
Flinterman <i>et al.</i> (2006) [39]	23	0.100–>3.0
Peeters <i>et al.</i> (2007) [24]	26	0.012–4.412 ²
<i>Cows' milk</i>		
May (1976) [32]	1	2.0
Bernstein <i>et al.</i> (1982) [46]	2	14.1
Moneret-Vautrin <i>et al.</i> (1995) [34]	5	8.0–200
Fiocchi <i>et al.</i> (2003) [35]	12	0.012–0.180
Morisset <i>et al.</i> (2003) [7]	59	0.0001–0.200
Meglio <i>et al.</i> (2004) [33]	18	?–0.090 ³
Rolinck-Werninghaus <i>et al.</i> (2005) [47]	1	0.150
<i>Egg</i>		
May (1976) [32]	4	0.200–2.0
Atkins <i>et al.</i> (1985) [45]	1	50
Moneret-Vautrin <i>et al.</i> (1995) [34]	8	0.020–15
Morisset <i>et al.</i> (2003) [7]	125	0.002–>7.11
Rolinck-Werninghaus <i>et al.</i> (2005) [47]	2	0.013–0.200
Buchanan <i>et al.</i> (2007) [36]	6	0.018–1.01
<i>Hazelnut</i>		
Ispano <i>et al.</i> (1998) [38]	21	1.50–20 ²
Wensing <i>et al.</i> (2002) [37]	31	0.001–0.100 ²
Flinterman <i>et al.</i> (2006) [39]	12	0.100–>3.0 ²
<i>Soybean</i>		
Magnolfi <i>et al.</i> (1996) [40]	8	0.088–3.6
Fiocchi <i>et al.</i> (2003) [35]	18	0.012–0.180 ⁴
<i>Mustard</i>		
Rance <i>et al.</i> (2000) [41]	15	0.001–0.936
Figueroa <i>et al.</i> (2005) [42]	14	0.045–0.493
<i>Fish</i>		
Hansen and Bindslev-Jensen (1992) [43]	7	0.006–6.656
Helbling <i>et al.</i> (1999) [44]	6 (cod)	1.0–64
	5 (catfish)	0.25–64
	3 (snapper)	1.0–4.0
<i>Sesame seed</i>		
Morisset <i>et al.</i> (2003) [7]	12	0.030–? ⁵
<i>Shrimp</i>		
Bernstein <i>et al.</i> (1982) [46]	1	14
Atkins <i>et al.</i> (1985) [45]	4	25–100

¹ MED: minimal eliciting dose (LOAEL) expressed in grams of the food as administered in the challenge trial (not normalized for protein content).

² Subjective symptoms as endpoint for some challenges in the group.

³ Lowest doses of milk impossible to quantify (drop).

⁴ Dose of soybean formula.

⁵ Highest MED for sesame seed was not given.

is about 50% protein. In some studies, subjective responses, such as oral allergy syndrome, were used as the criterion for a positive response [25,38]. In other studies, LOAELs were reported on the basis of objective reactions [7,30].

A binomial probability approach has been considered as one way to estimate the population-based threshold [8]. In this approach, 29 patients allergic to a particular food are challenged in a low-dose manner to identify a dose below which none of the 29 patients experiences an adverse reaction. Binomial probability theory then allows the conclusion that there is 95% certainty that fewer than 10% of this food-allergic population will react to ingestion of this dose of the particular food [8]. Of course, the group of 29 subjects must be representative of the entire allergic population. Furthermore, this approach allows for the possibility that almost 10% of patients allergic to that food will react to ingestion of that dose and this possibility may be considered as too high. Modeling of collective data from several studies is probably the preferred approach to determine the population-based threshold, although the best statistical model to use remains to be determined [8].

Usefulness of individual thresholds for reactivity

Knowledge of an individual patient's threshold dose allows the allergist to provide the patient with more useful advice. While all food-allergic patients should employ avoidance diets, patients with comparatively low threshold doses are at greater risk because exposure to small residual amounts of allergenic foods is more likely to provoke an adverse reaction. These individuals must be extremely vigilant because shared utensils, cooking vessels, and frying oil might be expected to transfer milligram quantities of the allergenic food. Even kissing someone who has consumed the allergenic food may pose a risk [48,49].

Low-dose oral challenges allow determination of an individual's threshold dose for reactivity via ingestion. Anecdotally, food-allergic individuals have also reacted to exposure to very small quantities of allergenic foods through other routes such as skin contacts with food surfaces, inhalation of vapors from cooking of the food, and exposure to dust in airplane cabins [3,50,51]. Routes of exposure other than the oral route, for example inhalation or skin contact, may be comparatively more sensitive, although this has not been carefully studied. Thus, knowledge of the oral threshold dose may be of limited value in providing advice regarding other routes of exposure.

Infants and children are sometimes able to outgrow their food allergies apparently through the development of oral tolerance [5]. That is particularly true for milk, egg, soybean, and wheat allergies [5]. Although not carefully studied in a longitudinal manner, the individual thresholds of these children appear to increase until they can tolerate

typical servings of these foods. Thus, it is tempting to speculate that those individuals with very low individual threshold doses would be less likely to outgrow their food allergy or would require a longer time period for that to occur.

In at least one study [25], individuals with histories of severe food allergies had significantly lower individual threshold doses. Perhaps this observation should not be surprising, because exposure to small amounts of the allergenic food is likely to elicit reactions in such individuals and inadvertent exposure to large doses seems likely to provoke more serious manifestations. Because of their vulnerability to small doses of hidden allergens, individuals with comparatively low threshold doses should probably be among the patients who would benefit the most from carrying an emergency epinephrine kit. However, in other studies [18], the correlation between the severity of reactions suffered in the community and the severity of reactions elicited during low-dose challenges was poor. The doses involved in reactions occurring in the community are certainly not controlled and could affect attempts to make such correlations. Such observations do indicate the value of clinical conservatism in decisions about access to epinephrine.

Food industry and regulatory uses of threshold information

Unfortunately, scientific and regulatory consensus does not exist to allow the establishment of population-based threshold levels. Many reasons exist for the lack of consensus, but key issues are the lack of data due to the relatively low numbers of patients with known and published individual threshold doses, the lack of individual NOAELs even in cases where the individual LOAEL is published, uncertainties emanating from the possible exclusion of patients with histories of severe reactions from challenge trials, and uncertainties due to differences in clinical protocols for low-dose challenges.

Governmental regulatory agencies could make effective use of population-based thresholds. Regulatory agencies have the responsibility to assure the safety of the food supply in their country or region. Certainly, undeclared major allergens in packaged foods should be considered as a potential health hazard for consumers with that food allergy. Recalls of products from the marketplace are common in some countries (United States, Canada, and Australia) as a result of undeclared allergens. Currently, any level of an undeclared allergen can be the basis for a recall. With the establishment of population-based thresholds, enforcement could be focused on products with undeclared allergens at levels likely to exceed these thresholds.

The food industry has the responsibility for maintaining effective allergen control in their manufacturing facilities to assure the safety of food-allergic consumers. However, economic efficiencies mandate the use of shared equipment and shared facilities between more allergenic and less allergenic formulations. The establishment of population-based

thresholds would allow the food industry to establish uniform and appropriate guidelines for evaluation of the effectiveness of their allergen control programs. Methods currently exist that allow the detection of residues of many commonly allergenic foods at ppm (μg per gram) levels [52]. The effectiveness of sanitation is often confirmed with these methods. However, the establishment of population-based thresholds would assure that these existing methods are sufficient to mitigate any possible hazards from allergen cross-contact.

The use of advisory labeling (e.g. “may contain peanut”) has proliferated on packaged foods in recent years. Many foods have such labels even though allergen residues cannot be detected in those foods [53]. Food-allergic consumers should be advised to avoid products bearing such advisory statements but evidence indicates that these consumers are increasingly ignoring these statements [53]. These advisory labeling statements are voluntary and companies have widely differing criteria for the use of such statements on packages. The establishment of population-based thresholds could be used by regulatory agencies as the basis for criteria for the use of advisory labeling statements. Such action would likely curtail the rampant use of such labeling and improve the quality-of-life of consumers with restricted avoidance diets.

“Allergen-free” products are also appearing on the market in many countries. The use of such labeling is voluntary and not well regulated in most circumstances. While consumers probably believe that no residues of the allergenic food are present in such products, that belief is not documented in the case of most of these products. The establishment of population-based thresholds could provide the basis for “allergen-free” products. The use of gluten-free labeling on products for the benefit of patients with celiac disease is a good example of the use of such labeling and regulation. The regulatory standards for gluten-free products are variable around the world but range from <20 to <200 ppm gluten. Products containing <100 ppm gluten appear to be safe for the majority of celiac patients [54]. Thus, the establishment of a regulatory, population-based threshold based on clinical science has allowed the prudent development of a gluten-free market category that benefits these patients.

Conclusions

Diagnostic challenge procedures for food allergy could allow physicians to determine the individual threshold doses for patients. As it stands, most food-allergic patients do not know their individual threshold dose because few allergy clinics make this assessment. The knowledge of individual threshold doses would allow physicians to offer more complete advice to food-allergic patients in terms of their comparative vulnerability to hidden residues of allergenic foods. The clinical determination of large numbers of individual threshold doses would allow estimates of population-based

thresholds using appropriate statistical modeling approaches. The food industry and regulatory agencies could also make effective use of information on population-based threshold doses to establish improved labeling regulations and practices and allergen control programs.

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