Standardization, validation and outcome of double-blind, placebo-controlled food challenges in children
Vlieg-Boerstra, Berber

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Chapter V

Ready-to-use introduction schedules for first exposure to allergenic foods in children at home

Berber J. Vlieg-Boerstra¹
Anthony E.J. Dubois¹
Sicco van der Heide²
Charles M.A. Bijleveld³
Saskia A.A. Wolt-Plompen¹
J.N.G. Oude Elberink²
Jeanet Kukler¹
Désirée F. Jansen⁴
C. Venter⁵
Eric J. Duiverman¹

¹Department of Paediatrics, Division of Paediatric Pulmonology and Paediatric Allergy, ²Department of Internal Medicine, Division of Allergy, ³Department of Paediatrics, Division of Paediatric Gastroenterology (at the time of this study), ⁴Department of Epidemiology and Bio-Informatics, University Medical Centre Groningen, University of Groningen, the Netherlands ⁵The David Hide Asthma and Allergy Research Centre, St Mary’s Hospital, Newport, Isle of Wight, UK.

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Chapter V

ABSTRACT

**Background:** The vast majority of children will undergo their first exposure to common allergenic foods at home. However, first exposure may lead to clinical reactions. It has been proposed to introduce allergenic foods gradually into the diets of children at risk for food allergy, but no practical dietary advice has been devised.

**Objective:** The aim of this study was to devise safe introduction schedules for common allergenic foods for use at home, based on the challenge doses as administered in DBPCFCs in children never previously exposed to these foods.

**Methods:** Seventy two double-blind, placebo-controlled food challenges (DBPCFCs) were performed in 63 children as a first known exposure. The incrementing challenge doses were converted into equivalent portions of these foods in their usual household form and incorporated in introduction schedules. The feasibility of the introduction schedules was tested in parents of children attending our clinic.

**Results:** Based on the results of the positive challenges (37) in which severe reactions did not occur, detailed introduction schedules and a reference photograph of the required increasing amounts of food were devised for use at home. Feasibility testing showed that, when using these introduction schedules, parents portioned initial doses significantly lower than without detailed instructions.

**Conclusions:** The introduction schedules and reference photograph provide information for parents to introduce the required amounts of allergenic foods in initial low doses at home. This may be expected to improve the safety of this procedure.
INTRODUCTION

The vast majority of children, including those who are at risk for food allergy, will undergo their first exposure to common allergenic foods, such as cow’s milk, egg, peanut and tree nuts at home. However, it is known that the first exposure to foods may lead to clinical reactions, both in food challenge studies and uncontrolled conditions\(^1\)\(^-\)\(^5\). Severe and potentially life-threatening reactions following such first exposures in uncontrolled conditions have been reported\(^1\). In a study by Sicherer et al\(^1\) it was shown, that the majority of the initial reactions occurred at home (72%). Similar figures were found in the UK in children developing peanut allergy\(^6\). While ideally all such children should undergo their first exposure to allergenic foods under medical supervision, or undergo skin testing and/or specific IgE determination for further risk stratification, it is clear that such a recommendation is unachievable. The physician’s assessment, taking account of the patient’s age, co-existing asthma, and the food to be introduced (peanuts/nuts vs other foods)\(^7\)\(^-\)\(^9\), may lead to the recommendation that introduction should either occur under medical supervision, or at home. Current guidelines recommend the introduction of these common allergenic foods gradually and individually into the diets of infants at risk for atopic disease\(^10\), but no practical advice as to how this may be done safely has been developed so far. Furthermore, little is known about the eliciting dose at first known exposure upon which safe dietary advice may be based. Thus, while medical supervision may be needed for children with the highest risk, providing guidelines with improved safety for home introduction of allergenic foods is equally important.

In general, the lower the dose, the less severe the symptoms\(^11\). Therefore, the incremental scales of food challenges, provided that no severe reactions occurred, may serve as the basis for these introduction schedules for children eligible to introduce at home.

The aim of this study was to devise safe introduction schedules for common allergenic foods for use at home, based on the challenge doses as administered in DBPCFCs in children never previously exposed to these foods.

METHODS

Study population

All children at high risk for food allergy, who consecutively attended our paediatric allergy clinic between January 2003 and June 2006 for the assessment of possible food allergy, and who had never knowingly ingested the food in question before, were included in this study.

Children at high risk for food allergy were defined as children with manifestations of atopic disease (asthma, allergic rhinitis, eczema, food allergy to foods other than the food in question), and/or with at least one first-degree relative with atopic disease, and/or having sensitization to food as assessed by skin prick tests (SPT) or specific IgE.
Because of dietary preventive measures, the children had been adhering to a diet from birth in which certain known allergenic foods (cow’s milk, egg, peanut, hazelnut, soy or walnut) were avoided prior to this study. In some individuals, exposure to allergenic foods was even delayed until teenage. In all children, the dietary restrictions were imposed by other health care professionals or were initiated by the parents themselves in the past. Because of uncertainty as to whether the avoided foods would be tolerated, or because of positive SPTs or positive RAST results for the avoided foods, introduction was postponed. Elimination of the food in question was confirmed by an experienced dietician, as has been described previously\(^{12}\). Information on sex, age, allergic symptoms, family history (number of first degree family members with atopic dermatitis, asthma, rhinitis or food allergy) was obtained. This study was exempt from medical ethical approval, as DBPCFCs in these children were performed as a routine diagnostic test.

**Determination of sensitization**

Sensitization to the allergenic food in question was determined by SPT with commercially available extracts (ALK-Abelló, Hørsholm, Denmark) and CAP-RAST (Phadia AB, Uppsala, Sweden) within 3 months prior to the DBPCFC. SPTs were expressed both in mm and as Histamine Equivalent Prick (HEP)\(^{13}\). The HEP-index is computed by dividing the size of the wheal of the SPT of the food tested (mm) by the wheal of histamine of the SPT (mm). RAST-results of \(\geq 0.35\) kU/l and SPT-scores \(\geq 3\)mm were considered positive. Children showing either positive SPT or specific IgE or both to the food tested were considered to be sensitized to the food in question.

**Food challenges**

DBPCFCs with cow’s milk, egg, peanut, soy, hazelnut, and walnut were performed. Foods chosen for DBPCFC were those foods which had been eliminated from birth. DBPCFCs were performed and assessed as described previously\(^{14}\). Briefly, placebo and active challenges were administered in a random order, and were administered on separate days with at least two weeks interval in between. The incremental scale and total challenge doses used are shown in Table 1. At the lowest doses, doses were doubled, whereas the higher doses increased 4 to 5 fold. Time interval between two challenge doses was 30 minutes.

The challenge was discontinued when objective allergic symptoms occurred, or subjective allergic symptoms occurred twice on two successive administrations of the challenge material. Immediate symptoms were defined as symptoms occurring during the challenge or within 2 hours after the last challenge dose. Two days after each challenge session late onset reactions were recorded by telephone questionnaire. Late onset symptoms were defined as symptoms occurring between 2 and 48 hours after the last challenge dose. All challenge sessions were assessed according to a standardized algorithm. Forty-eight hours after the second challenge session, the code was broken and the outcome of the DBPCFC
Table 1. Incremental scales and challenge doses used in DBPCFCs

<table>
<thead>
<tr>
<th></th>
<th>Cow’s milk (ml~g)</th>
<th>Soy Milk (ml~g)</th>
<th>Egg (mg)</th>
<th>Protein equivalent (mg)</th>
<th>Peanut (mg)</th>
<th>Hazelnut (mg)</th>
<th>Walnut (mg)</th>
<th>Protein equivalent (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 1</td>
<td>0.05</td>
<td>0.05</td>
<td>13</td>
<td>1.75</td>
<td>6</td>
<td>12</td>
<td>12</td>
<td>1.75</td>
</tr>
<tr>
<td>Dose 2</td>
<td>0.1</td>
<td>0.1</td>
<td>27</td>
<td>3.50</td>
<td>12</td>
<td>25</td>
<td>23</td>
<td>3.50</td>
</tr>
<tr>
<td>Dose 3</td>
<td>0.4</td>
<td>0.4</td>
<td>108</td>
<td>14</td>
<td>48</td>
<td>100</td>
<td>93</td>
<td>14</td>
</tr>
<tr>
<td>Dose 4</td>
<td>2.0</td>
<td>2.0</td>
<td>538</td>
<td>70</td>
<td>241</td>
<td>500</td>
<td>470</td>
<td>70</td>
</tr>
<tr>
<td>Dose 5</td>
<td>10.0</td>
<td>10.0</td>
<td>2690</td>
<td>350</td>
<td>480</td>
<td>860</td>
<td>870</td>
<td>130</td>
</tr>
<tr>
<td>Dose 6</td>
<td>50.0</td>
<td>50.0</td>
<td>13460</td>
<td>1750</td>
<td>1206</td>
<td>2500</td>
<td>2330</td>
<td>350</td>
</tr>
<tr>
<td>Total</td>
<td>63.0</td>
<td>63.0</td>
<td>16830</td>
<td>2190</td>
<td>2000</td>
<td>4000</td>
<td>3800</td>
<td>570</td>
</tr>
</tbody>
</table>

Protein equivalent amounts of allergenic food were administered, except for the highest amounts of peanut, where the high amounts of peanut and nuts could not be validated. The total and maximum challenge doses were determined by the limitations of adequate blinding in sensory testing.

* 1 medium egg = 50 gram
** 1 peanut kernel = 290–400 gram

was assessed according to a standardized protocol\textsuperscript{14}.

**Design of introduction schedules and feasibility testing**

All challenge doses of the incremental scales used in DBPCFCs, as well as two additional higher challenge doses, were converted into equivalent portions of these foods in their usual household form. We examined foods likely to be frequently used by parents of young children (except for walnut), which are universally available, have standardized recipes, can easily be prepared in a household setting, and are acceptable for young children. We examined cow’s milk, soy milk, egg, peanut and nuts, as well as manufactured foods, such as sponge fingers, home made muffins, peanut butter\textsuperscript{15}, and Nutella\textsuperscript{©} (Ferrero). Foods in their most appropriate and practical household forms were incorporated in the home introduction schedules, taking into account the young age of most children in whom the introduction schedules are to be applied and the small amounts in which the portions have to be administered. The increasing portions of the introduction schedules were photographed (except for cow’s milk or soy milk) to visualise the required amounts (Figure 1).

Without providing detailed instructions other than to introduce these foods gradually in increasing amounts, we then asked 10 parents of children who were attending our clinic for DBPCFC, how much and in which form they would administer cow’s or soy milk, egg, peanut, hazelnut or walnut as a first known exposure.
Finally, in these 10 parents, we tested the feasibility of the introduction schedules for the lowest portions (doses 1 and 2 for cow’s milk, doses 1 to 3 for egg, doses 1 to 4 for peanut, doses 1 and 2 for hazelnut, and doses 1 to 3 for walnut) (Figure 1 and Appendix A). We examined whether these parents were able to portion these foods with sufficient accuracy to ensure the safety of the procedure. The feasibility testing was done in the Food Challenge Unit of our clinic under supervision of one of the staff members. The staff member explained the purpose of the introduction schedules to the parents. Subsequently, she asked the parents to portion the required doses using the written instructions from Appendix A and, for the solid foods, the photograph as shown in Figure 1. She did not demonstrate...
the portioning, nor did she train the parents in using the introduction schedules or intervene during the feasibility testing by the parents. The parents were not allowed to practice first. For the portioning of cow’s milk and soy milk, we asked the parents to use a medicinal dropper. As indicated in Appendix A, a sharp knife was provided to portion the lowest doses of egg and peanut. For the portioning of Nutella, a type of knife as shown in figure 1 was provided for the testing. We ascertained the accuracy of the portioning by weighing.

Statistics
The Chi-square test (SPSS Software, 14th edition, SPSS Inc, Chicago III, USA) was used to analyse differences between the rate of positive results of DBPCFCs performed in sensitized and non-sensitized children. The Wilcoxon Signed Rank test was used to analyse differences between portions of allergenic foods administered by parents with and without instructions. Differences in mean age between the age of children having positive and negative challenges was determined by the two sample t test (two sided) (normally distributed).

RESULTS

Patients’ characteristics
A total number of 72 DBPCFCs were performed in 63 children: nine children underwent more than one DBPCFC with different foods. The characteristics of the patients who underwent the 72 DBPCFCs are shown in Table 2.

Table 2: Characteristics of 72 DBPCFCs

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>males</td>
<td>46 (64%)</td>
</tr>
<tr>
<td>females</td>
<td>26 (36%)</td>
</tr>
<tr>
<td><strong>Age (yrs), median (range)</strong></td>
<td>5.7 (0.7-15.9)</td>
</tr>
<tr>
<td><strong>Atopic disease at time of challenge, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>48 (67%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>45 (63%)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>28 (39%)</td>
</tr>
<tr>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td><strong>1st degree family member with atopy, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14 (19%)</td>
</tr>
<tr>
<td>≥1</td>
<td>58 (81%)</td>
</tr>
<tr>
<td><strong>Degree of sensitisation to the food in question, median (range)</strong></td>
<td></td>
</tr>
<tr>
<td>SPT (mm) (n =67 )</td>
<td>4 (0 - 19)</td>
</tr>
<tr>
<td>SPT (HEP) (n = 67)</td>
<td>0.8 (0 - 2.5)</td>
</tr>
<tr>
<td>Specific IgE (kU/l (n = 65)</td>
<td>1.71 (0 - &gt; 100)</td>
</tr>
<tr>
<td><strong>Sensitization rate, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>sensitized</td>
<td>57 (79%)</td>
</tr>
<tr>
<td>non-sensitized</td>
<td>15 (21%)</td>
</tr>
</tbody>
</table>
Food challenges
A total number of 37/72 challenges (51%) were positive. Positive DBPCFCs were found for cow’s milk (n = 6 out of 10), egg (n = 8 out of 19), peanut (n = 18 out of 26), soy (n = 1 out of 7), hazelnut (n = 3 out of 9), and walnut (n = 1 out of 1). There were no significant differences in age between children having a positive and negative DBPCFC. Positive DBPCFCs occurred in 33/57 sensitized cases (58%), and in 4/15 cases not sensitized to the food in question (27%). These frequencies were significantly different (p = .043).

Type of symptoms
The type of symptoms observed in positive challenges were dermal (54%), gastrointestinal (49%), local and upper airway (49%), lower airway symptoms (11%), accompanied by other symptoms, such as drowsiness and irritability in 43% of the challenges.
No severe symptoms or signs of difficulty in swallowing, stridor, hoarseness, or anaphylaxis occurred. No epinephrine was administered. In 30/37 positive active food challenge sessions, immediate symptoms occurred (within two hours after the last challenge dose), whereas in 7/37 positive active food challenge sessions, only late onset symptoms were reported by the parents (2 – 48 hours after the last challenge dose).
In cases in which only late onset symptoms were observed, dermal symptoms were reported in 3 cases (exacerbation of eczema, rash), gastro-intestinal symptoms in 4 cases (cramp, diarrhoea), and lower airway symptoms in 1 case (coughing, wheezing).
In two cases, a positive diagnosis could be refuted because of placebo reactions.

Figure 2: Cumulative eliciting doses (mg) of allergenic foods in positive DBPCFCs
Eliciting doses
In Figure 2, the cumulative eliciting doses as administered in the DBPCFCs are expressed in amounts of food (mg). For egg, peanut and walnut, the lowest eliciting doses were observed (dose 1), while in cow’s milk, soy and hazelnut, the most sensitive children reacted to dose 4. In DBPCFCs performed in sensitized children showing positive SPTs and/or positive RAST results to the food in question, the eliciting doses ranged from dose 1 to dose 6, whereas in DBPCFCs performed in non-sensitized children, all reactions occurred to dose 6. All children with late onset symptoms reacted to dose 6.

Introduction schedules and feasibility testing
In Appendix A the home introduction schedule with selected foods is shown. In Figure 1, a reference photograph of the increasing amounts of the solid foods of Appendix A. Introduction schedules for common allergenic foods for introduction at home (see also Fig 1).

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose 1</td>
<td>Dose 2</td>
<td>Dose 3</td>
</tr>
<tr>
<td>cow's milk or soy milk</td>
<td>1 drop</td>
<td>2 drops</td>
<td>8 drops</td>
</tr>
<tr>
<td>hard boiled egg</td>
<td>1 very small crumb of egg white</td>
<td>1 small crumb of egg white</td>
<td>1 crumb of egg white</td>
</tr>
<tr>
<td>peanut and peanut butter</td>
<td>1 very small crumb of peanut</td>
<td>1 small crumb of peanut butter</td>
<td>1 small knife-point of peanut butter</td>
</tr>
<tr>
<td>Nutella © and hazelnuts</td>
<td>1 small knife-point of Nutella</td>
<td>1 knife-point of Nutella</td>
<td>1/8 teaspoon of Nutella</td>
</tr>
<tr>
<td>walnut</td>
<td>1 very small crumb of walnut</td>
<td>1 small crumb of walnut</td>
<td>1 crumb of walnut</td>
</tr>
</tbody>
</table>

1 To be administered by a medicinal dropper
2 Crumbs of egg, peanut and walnut can be obtained by using a sharp and pointed knife.
3 To be administered using a measuring spoon set: 1/8 teaspoon = 0.625 ml; ¼ teaspoon = 1.25 ml; ½ teaspoon = 2.5 ml
4 To be administered by a kind of knife as shown on the photograph

For optimal safety, one to 3 doses may be administered on one day, with a time interval of at least one hour in between the doses.
When allergic symptoms occur, the introduction should be terminated, and a physician should be contacted.
the incremental scales is shown. From Appendix A and Figure 1 it becomes clear, that the lowest doses of these introduction schedules consist of very small amounts of allergenic foods. For cow’s milk and soy, the lowest doses consist of 1 drop of cow’s milk or one drop of soy milk. For solid foods, the lowest doses consist of crumbs of the allergenic food, equivalent to milligrams of food.

The median portions the parents would administer as a first exposure without detailed instructions are shown in Table 3 (not normally distributed). These amounts of foods were ascertained by weighing. For cow’s milk or soy milk, median portions were similar to the reference (i.e. doses 1 of the introduction schedule). For egg, hazelnut and walnut these median portions were at least approximately 8 times higher than the references. For peanut, the median portion was 25 times higher. Especially in the form of peanut butter, parents portioned relatively great amounts.

Table 3. Amounts of allergenic food (mg or ml) administered by parents with and without detailed instructions

<table>
<thead>
<tr>
<th>Food</th>
<th>Administration without detailed instructions dose 1</th>
<th>Administration using instructions from Appendix A and figure 1 dose 1</th>
<th>dose 2</th>
<th>dose 3</th>
<th>dose 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median (range) ref</td>
<td>median (range) ref</td>
<td>median (range) ref</td>
<td>median (range) ref</td>
<td>median (range) ref</td>
</tr>
<tr>
<td>cow’s/soy milk</td>
<td>0.08 (0.05 – 30) 0.05</td>
<td>0.05 0.05</td>
<td>0.1</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Egg</td>
<td>108* (27-2690) 13</td>
<td>11.5* (2-31)</td>
<td>15.5</td>
<td>35</td>
<td>108</td>
</tr>
<tr>
<td>Peanut</td>
<td>150** (6-2600) 6</td>
<td>6.5** (1-32)</td>
<td>8</td>
<td>45</td>
<td>175</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>(9-107)</td>
<td>260^</td>
</tr>
<tr>
<td>Hazel-nut</td>
<td>100 (12-520) 12</td>
<td>52 (11–90)</td>
<td>177</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Walnut</td>
<td>93*** (12-470) 12</td>
<td>11.5*** (2–41)</td>
<td>23</td>
<td>48</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2–51)</td>
<td>(20-235)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

* p = .011
** p = .021
*** p = .038
1. 100 mg Nutella is protein equivalent to 12 mg hazelnut
2. 200 mg Nutella is protein equivalent to 25 mg hazelnut
3. 50 mg peanut butter is protein equivalent to 48 mg peanut
4. 260 mg peanut butter is protein equivalent to 241 mg peanut butter
n.a.= applicable
The amounts of the foods the parents portioned when using the written instructions of the introduction schedules (Appendix A) and the photograph in Figure 1, with use of a medicinal dropper for cow’s milk or soy milk, are also shown in Table 3 (not normally distributed). These amounts of foods were also ascertained by weighing. For all 140 portions, the median amounts were similar to or smaller than the reference amounts of foods. The median of doses 1 of egg, peanut and walnut when portioned using the introduction schedules were significantly lower than when portioned without detailed instructions (p = .011, .021, and .038 respectively).

In 105/140 (75%) portions, the absolute weighed amounts were similar to or lower than the reference amounts of food, i.e. the required amounts of foods used in the introduction schedules (data not shown). In the remaining 35/140 (25%) portions, the absolute weights exceeded the reference amounts, but not for cow’s milk and soy. These greater amounts exceeded the required amounts of food by no more than one dose of the incremental scale used in DBPCFCs.

**DISCUSSION**

In our study, we devised ready-to-use home introduction schedules for common allergenic foods in young children designed to avoid severe reactions at first exposure. Although it may be a matter of debate in which children these guidelines are to be used, they could be recommended for any child at risk who does not warrant first exposure under medical supervision. Since there is no consensus about the clinical characteristics of children who should introduce allergenic foods at home, and which children should be challenged under medical supervision because of a significant risk for (severe) allergic reactions, additional studies are needed to answer this question. Although increasingly higher values of food-specific IgE are strongly associated with an increasing probability of clinical reactivity to food\(^{16}\), they are not associated with the severity of a reaction. In only one study an association was found between specific IgE to peanut and the severity of reaction in DBPCFCs\(^{17}\). It is noteworthy that in this study the dose of allergen in DBPCFCs was considered and incorporated into the statistical model. However, several risk factors are known to be associated with severe reactions, such as the coexistence of asthma, adolescence or young adult age, reacting to trace amounts of the offending food, (suspected) allergy to peanuts or tree nuts, and distance to emergency medical care\(^ {7-9}\). The physician’s assessment of the individual child will decide whether the child should be referred for introduction under medical supervision or at home. The latter population will generally consist of children in whom there is an increased risk for food allergy, but in whom there is little suspicion for the specific food in question. These children may be found for example in primary or secondary care centres, or may have older siblings with food allergy or atopic parents. They may have atopic dermatitis, or may be known with allergy to foods unrelated to the foods in question, such as cow’s milk. Little is known about the eliciting dose at first known exposure to allergenic foods.
Our study shows that the eliciting dose may vary from very low doses in the most sensitive individuals, to the maximum challenge dose in less sensitive children. The lowest eliciting doses were found for egg, peanut and walnut (dose 1, which contained 13 mg of egg, 6 mg of peanut or 12 mg of walnut). Although we did not observe reactions to the lowest doses of cow’s milk, soy and hazelnut, we cannot exclude that some sensitive children might react to lower doses. We thus converted all challenge doses of all foods into the home introduction schedules.

Caffarelli et al.\textsuperscript{4} also reported low eliciting doses to freeze dried (raw) egg on first exposure in DBPCFC, ranging from 0.5 to 20 mg, presumably equivalent to 2 to 80 mg of fresh egg. Similarly, Lack et al.\textsuperscript{5} described eliciting doses ranging from 50 mg to 8g of peanut, but it is not clear in the latter study if 50 mg was the lowest challenge dose used.

Although we observed a large spectrum of symptoms, no severe symptoms occurred. Most symptoms occurred immediately (30/37 positive challenges). Anaphylaxis did not occur, and no patient required epinephrine. The most severe reactions seen in our study consisted of lower airway symptoms seen in a small number of children (4/37). These were easily controlled with bronchodilator therapy. Thus, using these introduction schedules is likely to contribute to avoiding severe reactions at home. Importantly, the parents of the children using the introduction schedules are instructed to terminate the introduction, as soon as allergic symptoms occur. Additionally, sufficiently long time intervals are important to avoid severe reactions. Consequently, we propose that one to a maximum of 3 doses should be administered on one day, with a time interval of at least one hour in between the doses when using the introduction schedules (Appendix A). However, the improved safety of these introduction schedules needs to be validated in further studies.

Without instructions, doses administered at home are likely to be much higher than the low doses we administered in DBPCFCs. From our data it becomes clear, that for egg, hazelnut and walnut, without detailed instructions, parents would administer median doses which are approximately at least 8 times higher than the first doses of the introduction schedules, and for peanut a median of 25 times higher.

The lowest challenge doses of our incremental scales represent very small amounts of foods in their normal household form. Therefore, in order to achieve very low initial doses, the gradual introduction of allergenic foods in the household setting, as has been proposed previously\textsuperscript{10}, should be accompanied by detailed instructions on administering these very small amounts of allergenic foods, as have been devised in this study.

We tested the feasibility of these introduction schedules in parents of allergic children. Our results showed that for all doses parents seemed capable of portioning the required median amounts of foods with great accuracy. They were all similar to or lower than the reference amounts. Furthermore, the median doses of egg, peanut and walnut when portioned using the introduction schedules were significantly
lower \( p = .011, .021, \) and \( .038 \) respectively) than when portioned without detailed instructions. We did not train the parents before using the introduction schedules, because the introduction schedules were meant to be usable for a large majority of parents without specific instructions. The types of knives we used for the portioning are commonly used in the home. With regard to the absolute required amounts, for cow’s milk and soy milk it seemed feasible to portion the smallest amounts using medicinal droppers, which are widely available. For the solid foods, in 75% of the portions it seemed feasible for the parents to estimate the required amounts of the incremental scale quite accurately. In 35/140 (25%) portions, the absolute weights exceeded the reference amounts, but the maximum doses administered by some of the parents were much lower than the maximum amounts administered without use of the introduction schedule, often by a factor of 10 to 100 fold. Altogether, for children introducing common allergenic foods at home, these introduction schedules provide instructions for parents which may be expected to improve the safety of this procedure by allowing the administration of the required amounts of allergenic foods in initially low doses.

**Conclusions:** Children may react to very small amounts of foods on first exposure. Consequently, the gradual introduction of common allergenic foods at home should start at very low initial doses. In this study, introduction schedules and a reference photograph of the incrementally increasing amounts of allergenic foods for use at home are described. These schedules provide instructions for parents to introduce the required amounts of allergenic foods in low initial doses at home with improved accuracy. This may be expected to improve the safety of this procedure.

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REFERENCES


