DOI 10.1002/mnfr.201200330 *Mol. Nutr. Food Res.* 2012, *56*, 1708–1714

RESEARCH ARTICLE

# High fat food increases gastric residence and thus thresholds for objective symptoms in allergic patients

*Alan Mackie[1], Andre Knulst[2], Thuy-My Le[2], Peter Bures[3], Louise Salt[1], E.N. Clare Mills[4], Paul Malcolm[5], Adrian Andreou[5] and Barbara K. Ballmer-Weber[3]*

[1] Institute of Food Research, Norwich Research Park, Colney, Norwich, UK
[2] Allergy Unit, Department of Dermatology, University Hospital Zurich, Zurich, Switzerland
[3] Department of Dermatology/Allergology, University Medical Centre, Utrecht, The Netherlands
[4] Manchester Interdisciplinary Biocentre, University of Manchester, Manchester, UK
[5] Norfolk & Norwich University Hospital, Colney Lane, Norwich, UK

Received: May 30, 2012
Revised: June 29, 2012
Accepted: July 30, 2012

**Scope:** We have tested the hypothesis that high fat foods such as chocolate induce reduced rates of gastric emptying in comparison to lower fat foods and that this can impact uptake of allergens and subsequent reactions in allergic patients.

**Methods and results:** In four volunteers, magnetic resonance imaging was used to measure gastric emptying of a series of nine doses of either dark chocolate bars containing 35% fat or a chocolate dessert containing 8% fat. Analysis showed a mean rate of decrease in gastric volume with an 8% fat dessert was 0.33 ± 0.09 mL/min compared to an average rate of increase in gastric volume of 0.09 ± 0.10 mL/min for the chocolate bars. In parallel, eight allergic patients were challenged for either peanut or hazelnut in the same two matrices and doses using a standardized protocol. A statistical analysis of the objective symptoms in the allergic patients showed that the chocolate bars gave a significantly higher threshold for objective symptoms than the dessert.

**Conclusions:** Chocolate bars induced lower gastric emptying rates and in food challenges with allergic patients gave a higher threshold of elicitation for objective reactions than a dessert.

**Keywords:**
Food allergy / Food challenge / Food matrix / Gastric residence / Threshold

## 1 Introduction

Nuts and peanuts, particularly when roasted, tend to be consumed in a range of food types. The rates of protein digestion from low fat foods such as certain sauces and high fat foods such as chocolate systems may be very different at least in part because of differences in gastric residence time. Rates of gastric emptying are controlled by several factors, such as meal viscosity [1] and nutrient type. Studies have shown that delivery to the small intestine of fatty acids generated in the stomach is one of the main factors controlling gastric emptying rate [2]. Normally, the oral cavity is the first site of contact with an allergen and that is why oral allergy syndrome (contact allergy of the oral mucosa) often appears as one of the first symptoms. However, the digestion of fat takes place primarily in the small intestine where the allergens are released and can interact with the immune system to cause allergic symptoms. As a result, gastric emptying into the small intestine could be important in defining the dose presented to the immune system and timing of allergic symptoms.

Allergic reactions to peanut are among the most severe of all food allergies [3] and inadvertent ingestion of peanut by peanut-allergic individuals is the leading cause of fatal food allergic reactions [4]. It has also been reported that exposure to trace amounts of peanuts can provoke allergic reactions in some peanut-allergic individuals [5]. This has resulted in peanut-allergic consumers increasingly restricting food choices, partly as a result of the proliferation of advisory labels such as "may contain peanuts" [6]. Other nuts are also problematic, and allergy to tree nuts has been seen as an increasing problem [7]. In particular, hazelnut has been shown as an important allergenic food [8]. Consequently, there is

**Correspondence:** Dr. Alan Mackie, Institute of Food Research, Norwich Research Park, Colney, Norwich NR4 7UA, UK
**E-mail:** alan.mackie@ifr.ac.uk
**Fax:** +44-1603 507723

**Abbreviations: DBPCFC**, double-blind placebo-controlled food challenge; **MRI**, magnetic resonance imaging.

 

a need to assess what levels of contamination represent a hazard to the allergic population as a whole but also at the level of the individual, where the burden of avoidance could be ameliorated by threshold-based advice on how to manage their condition [9].

While there is a poor correlation between the severity of reported reactions in the community and the severity of reaction elicited during low-dose double-blind placebo-controlled food challenges (DBPCFCs) with peanut [10], this still represents the most reliable source of data. Recent data have also shown that clinical sensitivity in DBPCFCs to peanut is associated with increasing age and higher levels of specific IgE [11]. It is well known that an additional complication is the number of factors that can affect the results of a food challenge [12] but it is unclear what effect the type of food used to deliver the challenge has on threshold value. There have only been a limited number of studies undertaken, such as that by Grimshaw et al. [13], which showed that challenge vehicles containing higher fat required higher doses to elicit a reaction and that the reaction tended to be more severe. This observation has been recognized as an issue when developing food challenge recipes [14] or undertaking food challenges whether for establishing eliciting doses [15] or just for diagnosis [16].

Magnetic resonance imaging (MRI) has previously been validated for measurement of gastric volumes, gastric emptying, intragastric distribution, and gastric peristaltic movement assessment [17–20]. Echoplanar imaging has until recently been the most commonly used MR technique for assessment of stomach emptying [1,21]. Sequences that provide greater anatomical detail such as TRUFISTP (Fast Imaging with Steady State Precession) can also provide detail of the gastric wall and good contrast between the stomach wall and meals. While it may be argued that gastric behavior may be different in healthy adults and those undergoing an allergic reaction [22], in this is unlikely to be the case prior to any reaction and in this article we are interested in the role of the food matrix leading up to that first reaction.

In order to assess the effects of fat content discussed above, we have compared two different matrices, a water continuous mousse style dessert (DM, ~8% fat) and a fat continuous dark chocolate (CB, ~35% fat). The dessert system was developed for use in a multicenter study (EuroPrevall) looking at the prevalence of food allergy [23] and a description of the development is given elsewhere [24].

## 2 Materials and methods

### 2.1 Food material: dessert matrix and chocolate bar matrix

The materials used for both the MRI and the DBPCFC study comprised DM and a range of CB. The active materials for food challenge contained different amounts of the same peanut or hazelnut flour (Table 1). The DM made contains two different concentrations of the active ingredient as described elsewhere [24] and in Supporting Information. The CB was made by Nestlé Technical Centre in York using 60% cocoa mass, 36% sucrose, 4% cocoa butter, and trace amounts of orange oil as the placebo bar. The varying concentrations of peanut and hazelnut flour were added to the placebo chocolate. The bars were ascertained to be free from milk and the placebo bars to be free from the active ingredient.

### 2.2 MRI

In the gastric volume phase of the study, four healthy volunteers were invited on two separate days during which they underwent the same nine-dose schedule as the placebo day for allergic patients and with an MRI scan after each dose. The volunteers were randomly allocated either the DM or the CB on the first day and consumed the second matrix on the following visit. Placebo matrices were used in order to focus on the effect of fat content on gastric emptying. On each study day, volunteers underwent a preliminary MRI scan of the lower abdomen so that the level of gastric secretion could be assessed before the first dose was taken. Subsequently, after each dose (administered every 20 min), the volunteers were given another scan with two scans at 20-min intervals being taken after the last dose. While layering was observed for a number of the doses, particularly the later doses, we

**Table 1.** The composition of the nine doses used in the study protocol. The detailed composition of the CB and DM are given in Supporting Information

| Dose | Protein dose | Cumulative protein dose | Chocolate bars (Peanut/hazelnut) | Dessert |
|---|---|---|---|---|
| 1 | 3 μg | 3 μg | 1 g of bar 1 | 1 mL of 1:19 dilution of low |
| 2 | 30 μg | 33 μg | 1 segment (5 g) of bar 2 | 1 mL of 1:1 dilution of low |
| 3 | 300 μg | 333 μg | 1 segment of bar 3 | 5 mL low |
| 4 | 3 mg | 3.333 mg | 1 segment of bar 4 | 50 mL low |
| 5 | 30 mg | 33.333 mg | 1 segment of bar 5 | 6 mL of high |
| 6 | 100 mg | 133.333 mg | 1 segment of bar 6 | 20 mL of high |
| 7 | 300 mg | 433.333 mg | 1 segment of bar 7 | 60 ml of high |
| 8 | 1 g | 1.433333 g | 2 bars of 6 | 200 ml of high |
| 9 | 3 g | 4.433333 g | 2 bars of 7 | 2 top dose bars |

 

**Table 2.** Results of the double-blind placebo-controlled food challenges undertaken with both matrices. Light gray cells indicate subjective symptom threshold and dark gray cells indicate objective symptom threshold.

| Patient | Immuno CAP | Challenge matrix | Food | Dose 1 3 μg | Dose 2 30 μg | Dose 3 300 μg | Dose 4 3 mg | Dose 5 30 mg | Dose 6 100 mg | Dose 7 300 mg | Dose 8 1 g | Dose 9 3 g | Placebo result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 63.4 | Dessert | Peanut | - | - | - | OAS | OAS,G | OAS,G | OAS,G | U,G | ND | - |
| | | Bar | Peanut | - | - | - | - | OAS,G | OAS,G | OAS,G | F,G,C | ND | - |
| 2 | 47.6 | Dessert | Peanut | - | - | - | - | OAS,B,AE | ND | ND | ND | ND | - |
| | | Bar | Peanut | - | - | - | - | OAS | OAS | OAS,B,AE | ND | ND | - |
| 3 | 0.5 | Dessert | Hazelnut | - | - | - | - | - | OAS,C | OAS,C,R | OAS,C,R | OAS,C,R | - |
| | | Bar | Hazelnut | - | - | - | - | - | - | - | - | - | - |
| 4 | 55.7 | Dessert | Hazelnut | - | - | - | - | - | - | - | - | OAS, AE | - |
| | | Bar | Hazelnut | - | - | - | - | - | - | - | OAS | OAS | - |
| 5 | 10.9 | Dessert | Hazelnut | OAS | OAS | OAS,N | OAS,R | OAS | R | - | OAS,R | OAS,R | - |
| | | Bar | Hazelnut | - | - | - | - | - | - | - | OAS,R | OAS | - |
| 6 | 46.5 | Dessert | Hazelnut | - | R | - | - | OAS | OAS | OAS | - | OAS | PR, OAS dose 9 |
| | | Bar | Hazelnut | - | - | - | - | OAS | OAS | OAS | OAS | OAS | - |
| 7 | 19.7 | Dessert | Hazelnut | - | - | OAS | - | - | B | OAS,B | OAS,B | OAS | - |
| | | Bar | Hazelnut | OAS | OAS | OAS, TT | OAS | OAS | OAS | OAS | OAS | | - |
| 8 | 75.0 | Dessert | Hazelnut | - | - | OAS | OAS | OAS | OAS | OAS | OAS,N | OAS,R | - |
| | | Bar | Hazelnut | - | - | - | - | - | - | - | - | - | PR, OAS dose 3–9 |

The symptom codes are as follows: AE, angioedema; B, blisters of the oral mucosa; C, conjunctivitis; Co, cough; D, dyspnea; Dph, disphagia; F, flush; G, gastric pain and/or burning, abdominal pain; Gpru, generalized pruritis; Lpru, localized pruritis; N, nausea; OAS, oral allergy syndrome; PR, placebo reactor; R, rhinitis; U, urticaria; TT, tightness of the throat; ND, dose not given.

chose to measure only the total gastric contents. Approval for the study (09/H0310/18) was given by Norfolk Research Ethics Committee. Further details of the MRI are given in the Supporting Information.

### 2.3 DBPCFC

Two male and two female Swiss patients and four female Dutch patients were recruited from the Allergy Unit of the Department of Dermatology, University Hospital Zurich and from the Department of Dermatology/ Allergology of the University Medical Center Utrecht. The age of the subjects ranged from 22 to 51 with a mean of 32. All patients had a positive DBPCFC for peanut or hazelnut in DM and were additionally challenged with the CB. The results of serological analysis of the eight subjects are given in Table 2. At Zürich, two peanut allergic patients underwent challenges with the DM and the CB at an interval of 2–8 months and for hazelnut two patients were challenged with an interval of about 2 years. Both patients still reported symptoms upon accidental hazelnut ingestions before the second challenge. At Utrecht, four patients were challenged with hazelnut at intervals of 4–11 months. This study was approved by the local ethical committees of both hospitals.

A standardized DBPCFC protocol was used in which active and placebo were given on two different days. Thus for the matrix comparison study, volunteers came into the allergy clinics in Zurich and Utrecht on four separate days. Patients were randomly allocated to receive either active or placebo on the first day of the DM or CB challenge. In short, the protocol used a nine-dose schedule as laid out in Table 1, going from a low dose of 3 μg protein to a top dose of 3 g protein administered at 20-min intervals. The DBPCFC took place in the Allergy Clinics of the University Hospital Zurich and University Medical Center Utrecht, which are fully equipped for monitoring of vital signs and resuscitation. Challenges were discontinued in case of moderate/severe objective allergic symptoms. Patients were kept under observation for at least 2 h after the last dose.

### 2.4 Statistical analysis

A Wilcoxon paired *t*-test [25] was performed on cumulative threshold data for both object and subjective symptoms. The MRI data on gastric emptying rates were also assessed in this way and thus the significance of the differences seen was assessed.

## 3 Results

### 3.1 Gastric emptying

The gastric volume was determined from MRI scans taken periodically for each volunteer as described above. The cumulative volume of matrix consumed and gastric content volumes are shown for both the DM (Fig. 1) and the CB (Fig. 2). The difference between the cumulative dose and measured volume of gastric contents is also shown. It is clear that this difference in volume can only increase as a result of gastric secretion and can only decrease either as a result of gastric emptying or possibly as a result of absorption.

 

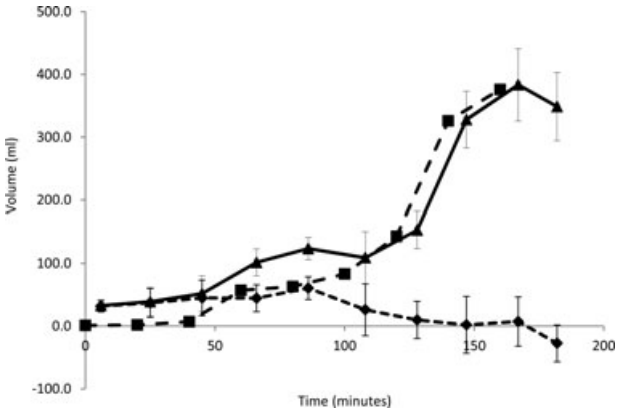


**Figure 1.** Data for the consumption of the DM. Mean volumes (mL) of the dose consumed (squares, course dash), gastric volume (triangles, continuous), and the mean difference between gastric and fed volumes (diamonds, fine dash). Lines are included to guide the eye only.

It should be noted that these events cannot be separated and that the volume difference is a combination of both secretion and emptying. The data presented represent the average volume data of the four volunteers.

At the start of the study, the volunteers were fasted and so the initial value of gastric volume represents the mean volume of secretion in the stomachs of the volunteers before the first dose was consumed. For the DM, the gastric volume remained higher than the volume consumed for the first five doses. After the sixth dose, there was on average a gastric emptying event so that subsequently the cumulative dose volume and the measured gastric volume were much closer. The overall pattern was one of gastric emptying at an average rate over the 3 h of $0.331 \pm 0.093$ mL/min ($p = 0.0011$).

The data for the CB were rather different as the gastric volume was significantly greater than the consumed volume

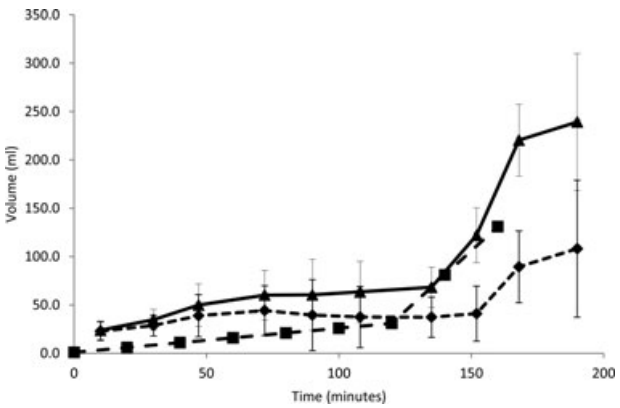


**Figure 2.** Data for the consumption of the CB. Mean volumes (mL) of the dose consumed (squares, course dash), gastric volume (triangles, continuous), and the mean difference between gastric and fed volumes (diamonds, fine dash). Lines are included to guide the eye only.

at all times, with little evidence of a major emptying event. The rate of gastric secretion remained very low until after the final dose, which induced a significant increase in secretions. The data overall showed gastric secretion at an average rate over the 3 h of $0.089 \pm 0.098$ mL/min ($p = 0.372$). Thus, the CB was characterized by secretion into the gastric compartment, while the DM was characterized by emptying of the gastric compartment.

### 3.2 Food challenges

Having shown that there was a difference in gastric residence time of the two matrices, we attempted to link the changes to the ability of the two matrices to elicit symptoms in allergic individuals. In the EuroPrevall project, partners challenged 135 patients for peanut and 132 for hazelnut, of these 56 (41%) and 91 (69%), respectively, were reactive. Additionally, 10% challenged with peanut and 13% challenged with hazelnut were placebo reactors. All adults in the EuroPrevall study were challenged with the DM and eight patients from two centers (Zurich and Utrecht) were also challenged with CB using the same dosing protocol (Table 1).

### 3.3 Peanut

Two of the patients challenged were with peanut in Zurich, Patients 1 and 2 had a history of moderately severe reactions. The results of the food challenges are given in Table 2 and show that in Patient 1 subjective symptoms developed earlier when peanut was administered in the DM rather than the CB but objective symptoms developed at the same dose in both DM and CB. In Patient 2, objective symptoms developed earlier in the DM than the CB.

### 3.4 Hazelnut

A total of six patients were challenged with hazelnut, Patients 3 and 4 were challenged in Zurich and Patients 5–8 were challenged in Utrecht. Both Patients 3 and 4 elicited objective symptoms only with the DM. Patient 3 did not respond with any symptoms to the CB challenge. Of the four patients challenged at Utrecht, Patient 8 responded to the placebo in the CB and Patient 6 reacted to the top dose in the placebo for the DM. Those patients reported mild subjective symptoms and were excluded from further analysis of the matrix for which they reacted to the placebo. In summary, in four of the six patients included, objective symptoms occurred at lower doses if hazelnut was delivered in DM rather than CB.

### 3.5 Threshold analysis

The data in Table 2 can be analyzed in terms of the threshold at which objective symptoms occurred. Subjective symptoms such as oral allergy syndrome were excluded as they are clearly

 

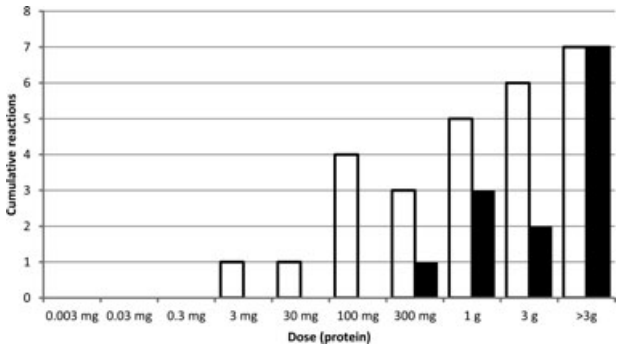


**Figure 3.** The cumulative threshold for objective symptoms comparing DM (white bars) and CB (shaded bars). The data include challenges undertaken in hazelnut and peanut allergic patients as shown in Table 2.

not systemic and thus not related to gastric emptying. Using the data for the seven DM where no placebo reactions were seen and the seven CB challenges where no placebo reactions were seen, the cumulative frequencies for objective reactions were calculated and the data are shown in Fig. 3. Where no reaction was seen, we have assumed that the threshold was in excess of the 3 g top dose as all patients reacted on at least one of the active days of DBPCFC and had a positive history and serology to the food. Where a dose was not given because the challenge had already been stopped at a lower dose, we have assumed that an objective reaction would have been elicited had the dose been given. As outlined above, there was a marked difference between the two matrices in terms of the thresholds for objective symptoms. Although the number of challenges was low and therefore the errors in data are relatively large, the result showed that the CB gave a higher threshold for objective symptoms than the DM ($p = 0.026$, Wilcoxon paired *t*-test).

## 4 Discussion

In this study, we have tested the hypothesis that high fat foods lead to an increased gastric residence time and that in fat continuous foods such as chocolate, this delays the presentation of protein to the immune system and thus the elicitation of systemic reactions in allergic individuals. We have compared the behavior of water continuous DM and fat continuous CB. The differences between the measured and fed volumes enabled the average gastric emptying or gastric secretion rate over the 3 h of the study to be calculated. The DM was emptied faster than the CB, in fact for the CB the mean gastric volume increased over what had been consumed giving a negative emptying rate over the 3 h. In an MRI study by Marciani et al. [26] an acid-unstable meal (in which the oil and water separated in the stomach) was found to empty faster (~3.8 mL/min) than a stable emulsion and in a similar study [27] the acid unstable meal was found to be less satiating. This result is consistent with the way that gastric emptying is controlled via gastrointestinal tract hormones such as cholecystokinin [28]. In the results presented above, we have clearly shown that gastric emptying of the higher fat CB was slowed, almost certainly through the cholecystokinin-controlled decrease in gastric emptying.

We have used two allergenic foods, peanut and hazelnut, to show that differences in the threshold of objective symptom elicitation between CB and DM are linked to the type of matrix that is used to deliver the allergen but not to the allergenic food itself. Due to logistical issues, the time between challenges with the two matrices has sometimes been rather long. Thus, if the threshold for eliciting objective symptoms changed between challenges the results would be biased, particularly in the light of observations that the eliciting dose of peanut in DBPCFC decreases with increasing age in children [11]. However, there is little evidence that the same is true in an older population. Conversely, repeated challenges close together could have elicited an immunotherapeutic effect in which the threshold was increased [29]. A gap of a few months removes this possibility. In the case of the two hazelnut allergic patients from Zurich where the gap was longer, both patients reported suffering from on-going food allergy at the second challenge according to accidental ingestion during the preceding year.

Of the 16 active challenges, there were two placebo responses (13%). This is in line with the rate observed in the whole Europrevall study, 14 and 15% for peanut and hazelnut, respectively, and similar to values quoted in the literature [30, 31]. The corresponding active challenge data were not analyzed. The results of statistical analysis showed that the CB gave a higher threshold for objective symptoms than the DM ($p = 0.026$, Wilcoxon paired *t*-test), in line with previous studies [13]. Analysis of the subjective symptoms showed no significant difference between the CB and DM. As stated above, this is most likely because the subjective symptoms represent local rather than systemic reactions and so are not as sensitive to the food structure or to gastric emptying. Given that there is a direct correlation between dose and severity of symptom, which is a basic tenet of food challenges [32], then one would also expect to see more severe symptoms elicited by the CB. However, because the patients were to be challenged multiple times, they were selected for their history of mild or moderate reactions. This and the limited number of subjects are most likely to be the reason for the lack of difference in the severity of symptoms elicited.

The data support the hypothesis that CB induces longer gastric residence and consequently elicits systemic allergic reactions more slowly than DM. This study shows the importance of understanding the relationship between what foods are eaten by allergic individuals in the community and the thresholds that are elicited in a clinical situation.

*The work described here was funded in part by the European Commission through the EuroPrevall project (FOOD-CT-2005-514000) and partly by the BBSRC through the Food Structure*

 

*ISPG. The MRI was funded by the NNUH Radiology Department research budget.*

*The authors have declared no conflict of interest.*

## 5 References

[1] Marciani, L., Gowland, P. A., Spiller, R. C., Manoj, P. et al., Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI. *Am. J. Physiol.-Gastr. L.* 2001, *280*, G1227–G1233.

[2] Karhunen, L. J., Juvonen, K. R., Huotari, A., Purhonen, A. K. et al, Effect of protein, fat, carbohydrate and fibre on gastrointestinal peptide release in humans. *Regul. Peptides* 2008, *149*, 70–78.

[3] Sicherer, S. H., Sampson, H. A., Food allergy. *J. Allergy Clin. Immunol.* 2010, *125*, S116–S125.

[4] Bock, S. A., Munoz-Furlong, A., Sampson, H. A., Further fatalities caused by anaphylactic reactions to food, 2001–2006. *J. Allergy Clin. Immunol.* 2007, *119*, 1016–1018.

[5] Taylor, S. L., Hefle, S. L., Bindslev-Jensen, C., Bock, S. A. et al., Factors affecting the determination of threshold doses for allergenic foods: how much is too much? *J. Allergy Clin. Immunol.* 2002, *109*, 24–30.

[6] Hefle, S. L., Furlong, T. J., Niemann, L., Lemon-Mule, H. et al., Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts. *J. Allergy Clin. Immunol.* 2007, *120*, 171–176.

[7] Zuidmeer, L., Goldhahn, K., Rona, R. J., Gislason, D. et al., The prevalence of plant food allergies: a systematic review. *J. Allergy Clin. Immunol.* 2008, *121*, 1210–1218.

[8] Osterballe, M., Mortz, C. G., Hansen, T. K., Andersen, K. E., Bindslev-Jensen, C., The prevalence of food hypersensitivity in young adults. *Pediatr. Allergy Immunol.* 2009, *20*, 686–692.

[9] Crevel, R. W., Ballmer-Weber, B. K., Holzhauser, T., Hourihane, J. O. et al., Thresholds for food allergens and their value to different stakeholders. *Allergy* 2008, *63*, 597–609.

[10] Hourihane, J. O., Grimshaw, K. E. C., Lewis, S. A., Briggs, R. A. et al., Does severity of low-dose, double-blind, placebo-controlled food challenges reflect severity of allergic reactions to peanut in the community? *Clin. Exp. Allergy* 2005, *35*, 1227–1233.

[11] van der Zee, T., Dubois, A., Kerkhof, M., van der Heide, S. et al., The eliciting dose of peanut in double-blind, placebo-controlled food challenges decreases with increasing age and specific IgE level in children and young adults. *J. Allergy Clin. Immunol.* 2011, *128*, 1031–1036.

[12] Hourihane, J. O., Knulst, A. C., Thresholds of allergenic proteins in foods. *Toxicol. Appl. Pharmacol.* 2005, *207*, 152–156.

[13] Grimshaw, K. E. C., King, R. M., Nordlee, J. A., Hefle, S. L. et al., Presentation of allergen in different food preparations affects the nature of the allergic reaction—a case series. *Clin. Exp. Allergy* 2003, *33*, 1581–1585.

[14] Vlieg-Boerstra, B. J., Herpertz, I., Pasker, L., van der Heide, S. et al., Validation of novel recipes for double-blind, placebo-controlled food challenges in children and adults. *Allergy* 2011, *66*, 948–954.

[15] Flinterman, A. E., Pasmans, S. G., Hoekstra, M. O., Meijer, Y. et al., Determination of no-observed-adverse-effect levels and eliciting doses in a representative group of peanut-sensitized children. *J. Allergy Clin. Immunol.* 2006, *117*, 448–454.

[16] Sicherer, S. H., Sampson, H. A., Peanut allergy: emerging concepts and approaches for an apparent epidemic. *J. Allergy Clin. Immunol.* 2007, *120*, 491–503.

[17] Ajaj, W., Goehde, S. C., Papanikolaou, N., Holtmann, G. et al., Real time high resolution magnetic resonance imaging for the assessment of gastric motility disorders. *Gut* 2004, *53*, 1256–1261.

[18] de Zwart, I. M., Mearadji, B., Lamb, H. J., Eilers, P. H. C. et al., Gastric motility: comparison of assessment with real-time MR imaging or barostat measurement—initial experience. *Radiology* 2002, *224*, 592–597.

[19] Kunz, P., Feinle-Bisset, C., Faas, H., Boesiger, P. et al., Effect of ingestion order of the fat component of a solid meal on intragastric fat distribution and gastric emptying assessed by MRI. *J. Magn. Reson. Imaging* 2005, *21*, 383–390.

[20] Marciani, L., Young, P., Wright, J., Moore, R. et al., Antral motility measurements by magnetic resonance imaging. *Neurogastroenterol. Motil.* 2001, *13*, 511–518.

[21] Marciani, L., Young, P., Wright, J., Moore, R. J. et al., Echo-planar imaging in GI clinical practice: assessment of gastric emptying and antral motility in four patients. *J. Magn. Reson. Imaging* 2000, *12*, 343–346.

[22] Arslan, G., Lillestol, K., Mulahasanovic, A., Florvaag, E. et al., Food hypersensitivity reactions visualised by ultrasonography and magnetic resonance imaging in a patient lacking systemic food-specific IgE. *Digestion* 2006, *73*, 111–115.

[23] Mills, E. N., Mackie, A. R., Burney, P., Beyer, K. et al., The prevalence, cost and basis of food allergy across Europe. *Allergy* 2007, *62*, 717–722.

[24] Cochrane, S. A., Wantling, E., Salt, L. J., Rogers, A. et al., Development of a standardised double-blind placebo-controlled vehicle for the EuroPrevall Project. *Allergy* 2012, *67*, 107–113.

[25] Wilcoxon, F., Individual Comparisons by ranking methods. *Biom. Bull.* 1945, *1*, 80–83.

[26] Marciani, L., Wickham, M. S. J., Bush, D., Faulks, R. et al., Magnetic resonance imaging of the behaviour of oil-in-water emulsions in the gastric lumen of man. *Brit. J. Nutr.* 2006, *95*, 331–339.

[27] Marciani, L., Wickham, M., Singh, G., Bush, D. et al., Enhancement of intragastric acid stability of a fat emulsion meal delays gastric emptying and increases cholecystokinin release and gallbladder contraction. *Am. J. Physiol.-Gastr. L.* 2007, *292*, G1607–G1613.

[28] Delzenne, N. M., Blundell, J., Brouns, F., Cunningham, K. et al., Gastrointestinal targets of appetite regulation in humans. *Obes. Rev.* 2010, *11*, 234–250.

 

[29] Anagnostou, K., Clark, A., King, Y., Islam, S. et al., Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin. Exp. Allergy* 2011, *41*, 1273–1281.

[30] Wensing, M., Penninks, A. H., Hefle, S. L., Koppelman, S. J. et al., The distribution of individual threshold doses eliciting allergic reactions in a population with peanut allergy. *J. Allergy Clin. Immunol.* 2002, *110*, 915–920.

[31] Vlieg-Boerstra, B. J., van der Heide, S., Bijleveld, C. M. A., Kukler, J. et al., Placebo reactions in double-blind, placebo-controlled food challenges in children. *Allergy* 2007, *62*, 905–912.

[32] Bock, S. A., Sampson, H. A., Atkins, F. M., Zeiger, R. S. et al., Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure—a manual. *J. Allergy Clin. Immunol.* 1988, *82*, 986–997.

 