Chapter I  General Introduction
1.1. Accumulating knowledge of food allergy during the last few decades

The understanding of allergic disease by the medical profession is a relatively young phenomenon. Although the technique of skin prick testing originated around 1880, the immunologic mechanism of this test and the diseases with which it was associated was unknown at that point. This lack of understanding was due to the fact that the causative immunoglobulin IgE was discovered only recently. The discovery of IgE had a significant impact on the understanding of the disease, because this greatly improved our understanding of allergic inflammation and diagnoses as well as treatment of allergic diseases. From that moment onwards, it was possible to quantify and measure sensitization in serum. With the discovery of IgE, it became obvious that certain symptoms could be caused by IgE directed towards specific foods in patients with food allergy. Along with the increasing knowledge about food allergy and the mechanisms behind the disease, different nomenclatures emerged over the years. Currently, according to an EAACI position paper, the main encompassing term of adverse reactions to food is “food hypersensitivity” (Figure 1). When immunologic mechanisms have been demonstrated, the appropriate term is “food allergy”, which can either be “IgE-mediated food allergy” or “non-IgE-mediated food allergy.”

All other reactions previously referred to as “food intolerance” should be referred to as “non-allergic food hypersensitivity”, but in practice, the term “food intolerance” is still being utilized. This thesis deals exclusively with IgE-mediated food allergy, which will be referred to as “food allergy”. Food allergy is an atopic disease. Atopy can be defined as a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhino conjunctivitis, or eczema/dermatitis. IgE-mediated food allergic patients, or simply food allergic patients, demonstrate IgE-mediated adverse reactions to the food in question, however, IgE may not always be demonstrable using current in vivo and in vitro assays. Although generally, the use of the internet has increased enormously during the

![Figure 1. Nomenclature for food hypersensitivity](image-url)
last decade, the increasing interest for and available data on food allergy may be reflected by the number of articles in Pubmed, which has steadily been increasing over the years, and is still increasing. When searching for “food allergy” OR “cow’s milk allergy” OR “food hypersensitivity” OR “adverse reactions and food”, a number of 94 publications can be found published in the year 1970, 134 articles in 1980, through 268, and 409 articles published in the years 1990 and 2000 respectively. In 2006, a total number of 640 papers were published.

Since more than half a century, the need for objective and unequivocal investigation techniques to study food allergy have been addressed and stressed by several authors. Before then, only articles and books on food allergy were published containing anecdotal, non-controlled reports of symptoms attributed to food allergy. At a food symposium during the 6th Annual Meeting of the American Academy of Allergy in 1950, Dr. F.C. Lowell opened an editorial with the following statement: “There is perhaps no field in medicine in which more divergent views are held than in that of allergy to food. In order to demonstrate a cause-and-effect relationship between food ingestion and symptoms, foods administered should be completely disguised, perhaps best in capsules or by stomach tube”. In another editorial by Dr. C.D. May, a few decades later, entitled: “Are confusion and controversy about food hypersensitivity really necessary?”, he explained that controversy about food allergy can only be removed by unbiased observations, which may only be obtained by the use of the double-blind, placebo-controlled food challenge (DBPCFC) (Box 1).

Initially, C.D. May introduced the DBPCFC in the mid-1970’s and, along with S.A. Bock, pioneered the use of the DBPCFC. This early work paved the way for several other investigators. A manual and methodological aspects of food challenge procedures were published in 1988 and 1990 respectively. In these documents, the practical basis for designing DBPCFCs is described. Many of the

**Box 1.**

*The Double-blind, placebo-controlled food challenge test (DBPCFC)*

In a DBPCFC, the patient is challenged with sequentially incrementing amounts of an active suspected allergenic food (or “verum”) and with a placebo food. The active and placebo challenges are conducted in random order and preferably on separate days. In earlier days, capsules were used to disguise the food. Currently, the active food is disguised in a test food matrix with similar sensory properties to the placebo test food. Both the patient and the physician are blinded for the sequence of the challenges, until the code is broken at the end of the test. In this test, the patient serves as his/her own control. The purpose of the DBPCFC is to document or refute a causative relation between the suspected food and allergic symptoms. Severity of symptoms should not be reproduced during DBPCFCs.
recommendations given in these publications are still being applied today in performing DBPCFCs. The DBPCFC has been regarded as the gold standard for diagnosing food allergy for over 20 years\textsuperscript{15,17,18}. The statements cited above by F.C. Lowell and C.D. May, as well as the following statement published in 1990 still hold today: “The DBPCFC is currently the only completely objective method for determining the validity of a history of an adverse reaction to a food”\textsuperscript{16}.

Over the years, lessons learned from the outcome of the DBPCFCs have been playing a crucial role in gaining evidence-based knowledge on food allergy\textsuperscript{19}. Reliable and unequivocal information and knowledge on all clinical aspects of food allergy can only be gained by well-conducted DBPCFCs. To date, indications for and purposes of food challenges tests may be 1. to establish or refute the diagnosis of food allergy, 2. to determine resolution or persistence of food allergy, 3. to determine thresholds in food allergic patients, and 4. to gain scientific knowledge and data on food allergy, such as documentation of novel reaction patterns to allergenic foods, and reactions to new allergens.

\textbf{1.2. Diagnosing food allergy in the Netherlands: From expert opinion towards evidence-based diagnostic procedures}

In the Netherlands, it was only in the late 1980’s that awareness of food allergy began to increase, and that physicians and dieticians accepted the concept, that common, normally healthy foods, could cause disease. The institution of the consumer’s association for food allergic patients, “The Nederlandse Voedselallergie Stichting” (NVAS; currently called: “Stichting Voedselallergie”), initiated by Mrs. Nardi Nieborg, mother of two food allergic children, brought together physicians and dieticians interested and somehow experienced in the field of food allergy. This resulted in a consensus report on food allergy and food intolerance\textsuperscript{20} a few years later. However, evidence based publications regarding DBPCFCs were scarce. In a workshop focusing on the methodology for clinical studies of adverse reactions to food\textsuperscript{16}, a total number of only 21 well-conducted clinical trials on food allergy could be retrieved from Pub med (1983 – 1988). This low number of studies illustrates that very little scientific knowledge was available at that time. In the Netherlands, the diagnosis and management of food allergy were based on expert opinion of physicians and dieticians. It was assumed, for example, that atopic infants were at risk for allergic reactions to “any” food or food components\textsuperscript{21}. To date, it has become clear that the majority of food allergic reactions in children is caused by a small number of foods\textsuperscript{7}. Also, a delayed introduction of common allergenic foods was generally regarded as effective in preventing food allergy in high risk infants, not only in the Netherlands but world wide\textsuperscript{22}. The latter concept is being challenged, as is discussed in Chapter VIII. DBPCFCs were performed only occasionally and in small numbers in a few of the University Medical Centres, such as Groningen,
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Utrecht and Rotterdam. To date, in the Netherlands DBPCFCs are performed on a regular basis as a routine diagnostic measure and for scientific purposes in an increasing number of centres\textsuperscript{23,24}. In 2001, at the University Medical Centre Groningen (UMCG), the Food Challenge Unit (FCU) was established by Prof. Dr. Anthony Dubois, allergist, and Dr. Charles Bijleveld, paediatric gastroenterologist, to diagnose food allergy in children.

The results as described in this thesis are obtained from approximately 500 DBPCFCs performed from 2002 until 2007 at the FCU of the UMCG.

1.3. Limited standardization and validation of the DBPCFC to date

Although the DBPCFC has been the diagnostic procedure of choice over the years, only few attempts have resulted in standardizing and validating (parameters of) the test procedure\textsuperscript{18,25,26} for clinical and scientific purposes. Despite guidelines for the administration of the test procedure\textsuperscript{15,16,18,27}, to date, no universal protocol for the performance of the DBPCFC has been established. Standardization and validation of DBPCFC procedures would clarify test procedures, and would facilitate comparing scientific results between different centres, would provide the highest diagnostic accuracy, greatest safety, optimal clinical and scientific information, and maximal convenience and patient acceptance. In 2001, Bindslev-Jensen\textsuperscript{28} stressed the fact that such standardization was much needed, and described several patient-related and procedure-related parameters of the DBPCFC, which should be agreed upon in a standardization procedure (Table 2).

In the position paper on oral food challenge procedures published a few years later
in 2004\textsuperscript{18}, proposals are made for standardization of the test procedure. However, despite the fact that it is not realistic to have standardized all parameters at all times for every individual patient, several crucial parameters of the DBPCFC procedure remain to be validated. Examples include incremental scales, total and maximum doses, the administration of active and placebo challenges (interspersed or active and placebo challenges administered on separate days), indications for DBPCFC (in contrast to indications for open food challenges), criteria to terminate the test, and assessment of test results. In a recent publication by Niggemann and Beyer\textsuperscript{29}, pitfalls in DBPCFCs such as a lack of uniform criteria to assess and terminate the challenge, are described, illustrating the fact that much work still remains to be done with regard to standardization of the test procedure.

1.4. Need for practical guidelines

Physicians and dieticians generally consider diagnosing food allergy as difficult, elusive and complicated. Recently, the Health Council of the Netherlands\textsuperscript{30} stated that the DBPCFC is the diagnostic procedure of choice for diagnosing food allergy, and that this test should become available for diagnosing food allergy in primary care. Currently, the awareness for the need of objective and unbiased diagnostic procedures in the Netherlands is increasing. Many tertiary and secondary centres, as well as primary health care centres have indicated interest in carrying out DBPCFCs to improve their diagnostic abilities in food allergic patients, and are currently attending workshops and educational sessions on DBPCFCs predominantly provided by the UMCG.

In many publications on food allergy, statements such as “The DBPCFC is the gold standard to establish the diagnosis of food allergy” appear in the text, suggesting that the DBPCFC is an often utilized, well-standardized and validated diagnostic procedure. However, in practice, the DBPCFC is conducted in only a limited number of centres, almost certainly due to several practical factors, such as the labour intensity of the test, lack of available challenge materials and incremental

\begin{table}
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\caption{Proposed parameters for standardization of the DBPCFC by Bindslev-Jensen in 2001\textsuperscript{28}}
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\textbf{Patient-related parameters:} & \\
- Selection of patients for challenges & \\
- The use of in vitro and in vivo tests for selection of patients & \\
- The nature of a suspected reaction & \\
\hline
\textbf{Procedure-related parameters:} & \\
- The source of food used for challenge & \\
- Starting dose used for challenge & \\
- Dose increment & \\
- Time interval during challenges & \\
- Top dose & \\
- Number of placebo and active challenges & \\
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scales, as well as standardized protocols focusing on assessment of reactions or termination of challenges. Additionally, the perceived risk of severe reactions and lack of compliance in some patients may make physicians hesitate to perform food challenge tests. Therefore, standardized protocols, educational materials, as well as recipes for challenge materials are much needed (Chapter II). This may help physicians and dieticians to set up food challenge tests by providing necessary tools. Finally, not all physicians are convinced of the added diagnostic value of the DBPCFC as compared to open food challenge tests, also due to lack of data in this respect. Especially in case of a convincing history of immediate and objective reactions to food, many health care professionals consider double-blind challenges unnecessary. Thus, convincing data on the necessity of randomized, double-blind, placebo-controlled tests may elucidate the value of unbiased and objective observations (Chapter IV).

1.5. Purpose of this thesis
The aims of this thesis were first, to standardize the procedure of the DBPCFC in children for the FCU of the UMCG, and to validate several parameters of the challenge procedure. Secondly, to examine the outcome of DBPCFC performed from 2002 until 2007 in subgroups of children and to formulate practical guidelines and recommendations for the management of food allergy in children.

1.6. Outline of this thesis
In Chapter II, the development and validation by sensory testing for difference of challenge materials for use in DBPCFCs is described. Recipes with cow’s milk, soymilk, egg, peanut, hazelnut, and wheat were first tested by volunteers from the hospital staff and subsequently by a professional panel of food tasters in a food laboratory designed for sensory testing.

In Chapter III, we comment on the method of sensory testing by other authors, using a non-professional panel of food tasters, which may overestimate the validity of recipes.

In Chapter IV, we analyze the occurrence and features of placebo events in DBPCFCs in children sensitized to the challenged food, and assess their diagnostic significance of the DBPCFC.

In Chapter V, we describe the development of introduction schedules for major allergenic foods for use at home, to be administered in children with an increased risk of food allergy, but who do not, according to the physician’s assessment, warrant food challenge testing. The incrementing amounts of these ready-to-use introduction schedules are based on incremental scales administered in DBPCFCs as a first known exposure, and their feasibility is demonstrated in the paper.

In Chapter VI, dietary assessment is described in children adhering to an allergen avoidance diet from birth, to analyze if elimination was complete and feasible, and
to investigate if dietary assessment can be used in predicting the outcome of the DBPCFC.

In Chapter VII, a study on consecutively performed DBPCFCs in children with a clear-cut history of anaphylaxis to food is described to determine whether the frequency of negative challenge tests in children with anaphylaxis to food is frequent enough to warrant challenge testing, and to document the safety of this procedure.

In Chapter VIII, the main results of this thesis are discussed. Finally, recommendations for future research are made.
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