FOOD STANDARDS AGENCY

Report of 2008 T07 Food Allergy and Intolerance Research Programme Review

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FOOD STANDARDS AGENCY

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1. Foreword

Allergy and intolerance to foods are important and not uncommon complaints. In line with its overarching strategy, the aim of the Food Standards Agency is to advise and protect food allergic and food intolerant individuals, and to assist them in making informed choices about the foods they purchase and consume. The Agency addresses these objectives in a number of ways, among which is commissioning of targeted research with the aim of ensuring that guidance and policies are based on sound scientific evidence and the best available information. Such research is managed through the Food Allergy and Intolerance Research Programme (T07).

The T07 Research Programme was launched in 1994 under the auspices of the Ministry of Agriculture Fisheries and Food, and was last reviewed formally in 2003. As many of the research projects commissioned since then have been completed, or are nearing completion, it was considered timely and appropriate to review again this year the relevance, productivity and effectiveness of the T07 Programme. This Review was conducted over 3 days during February 2008, and we are indebted to an independent Panel of acknowledged international experts, in various relevant disciplines, who were charged with evaluating the management and productivity of the T07 Programme during the preceding 5 years.

Within this report is a detailed summary of the research projects comprising T07 that were considered, the key issues that were discussed, and the conclusions and recommendations that were reached by the independent Panel. The review process was rigorous and structured, but nevertheless characterised by lively and informed debate. I am pleased that the Panel found that the research commissioned and conducted during the last 5 years has made significant contributions in areas relevant to the policy needs of the Agency. Included among these are our appreciation of the prevalence of food allergy in general, and of peanut allergy in particular, the immunological mechanisms through which allergic responses to dietary proteins are induced and regulated, and of the importance of route and timing of exposure on the acquisition of sensitisation to food proteins. Additionally, through T07, the Agency has addressed whether and to what extent food additives may impact on the behaviour of children.

Against this background the Panel also identified areas of potential importance that might inform the T07 Research Programme during the next 5 years, and these recommendations are also contained within this report.

Overall the exercise has once again served to provide the Agency with invaluable support and guidance in its continuing efforts to exploit fully for the benefit of consumers the fruits of previously commissioned Research Programmes, and to identify clearly our future needs in providing support and guidance to those with food allergy and food intolerance.

I look forward to being associated with the T07 Programme during the next 5 year period.

Professor Ian Kimber
T07 Programme Advisor

2. Executive Summary

Every 5 years the Food Standards Agency reviews individual Programmes of research that it has commissioned to evaluate its success and productivity. The Food Allergy and Intolerance Research Programme was reviewed in February 2008 with the aim of assessing the success of the Programme against its aims and objectives and considering the future direction of the Programme.

The Review meeting was held from the 19th – 21st February 2008. The first 2 days of the meeting were an open meeting consisting of presentations and discussions on T07 projects. The third day of the meeting was a closed session for the expert Review Panel, Agency officials and the T07 Programme Advisor, in which individual projects within the T07 Programme and the Programme as a whole were reviewed and recommendations were made.

It was considered by the Review Panel that the Research Programme had been successful in addressing the majority of its aims and that collectively the projects funded within the Programme over the last 5 years have significantly progressed the state of current scientific knowledge in a number of areas. It was considered by the Panel that not only had the research generally been conducted well but it had also delivered a large number of outputs which have been relevant to the Agency's policy and translated into sound consumer advice, particularly regarding the importance of dermal route of exposure in determining allergy or tolerance.

When considering the future direction of the Programme, the Panel suggested a number of areas of particular priority, including investigation of the mechanisms involved following environmental (including dermal) exposure to allergenic foods, the development of work to underpin the development of management thresholds for allergenic foods, and work to improve the reliability of methodologies for the detection and quantification of food allergens in food products. The Agency will take account of the valuable comments and recommendations that were made by the Review Panel about the performance, productivity and scientific quality of the Programme when determining its direction over the next 5 years.

3. Introduction

3.1 Food Allergy and Food Intolerance

It is necessary when considering food allergy and intolerance to distinguish carefully between the 2. Adverse reactions to food may take a number of different forms, including food intolerance, food aversion and food poisoning. Although these conditions are quite different, the symptoms can be quite similar. Food intolerance is an adverse reaction to food that is reproducible and takes place every time contact is made with a particular food or food ingredient. The reaction may involve the immune system, in which case it is known as a food allergy. It may also be caused by other things, such as a fault in the way the body breaks down food, which can be due to the lack of a particular enzyme, and this would be classed as a food intolerance. The exception to this definition is coeliac disease, an intolerance to dietary gluten, which does involve the immune system, although in a different way to food allergies.

Food intolerances are generally mediated by non-immunological mechanisms that occur following consumption of a particular food or food ingredient, and are generally not so severe or immediately life threatening as food allergies. However, food intolerance can still make someone feel ill and significantly affect longer term health and wellbeing.

It is particularly important for those consumers seeking to avoid certain foods or ingredients, such as those with a food allergy or intolerance, to be able to choose foods that are safe for them. Although most allergic reactions to food are mild, the severity of symptoms can vary and, in rare cases, allergic reactions to food can be fatal. Although these fatal reactions are not common, they do occur on a regular basis and not just to peanuts. Current estimates suggest that 1 to 2% of adults and 5 to 8% of children in the UK have a food allergy, with up to 1 in 55 children having a peanut allergy[1]. In the UK, at least 10 people are thought to die every year from an allergic reaction to food, although it is thought that the true figure is likely to be higher, and many more than this require emergency hospital treatment. This is in addition to the longer term health effects and impact on quality of life. In addition it is estimated that 1 person in 100 is intolerant to gluten[2].

The amount of an allergenic food required to provoke a reaction in a sensitive individual varies significantly from person to person and also over time depending on a range of factors. The most sensitive individuals can react to very small (microgram) amounts of an allergen.

[1] J. Hourihane, R. Aiken, R. Briggs, L. Gudgeon, K. Grimshaw, A. DunnGalvin, S. Roberts. (2007) **The impact of government advice to pregnant mothers regarding peanut avoidance on the prevalence of peanut allergy in United Kingdom children at school entry**. Journal of Allergy and Clinical Immunology, 119 (5), 1197–1202.

[2] Bingley, P. J. *et al.* (2004) **Undiagnosed coeliac disease at age seven: population based prospective birth cohort study**. British Medical journal **7435** 322–323.

3.2 Aim of the Agency's Work on Food Allergy and Food Intolerance

The Agency's work on food allergy and food intolerance aims to protect food allergic and food intolerant consumers and to help them to make informed choices about food[3]. We do this via 4 key strands of activities: 1) negotiating and implementing legislation to improve statutory controls on the labelling of food allergens, 2) provision of best practice guidance for industry and enforcement bodies to encourage greater awareness and control of food allergens through the food supply chain, 3) provision of advice about food allergy and intolerance to consumers and other stakeholders, and 4) commissioning scientific and consumer research on food allergy and intolerance to ensure that policies are based on robust scientific evidence.

3.3 The Food Allergy and Intolerance Research Programme (T07)

It is very important that the Agency bases its policies and advice on the best available science. In order to support its work on consumer protection, the Agency funds research on a wide variety of topics including food safety, nutrition, food authenticity, food quality issues and risk communication.

As part of its Research portfolio, the Agency has a Food Allergy and Intolerance Research Programme which funds ~£1million/year of fundamental, applied, clinical and social research on different aspects of food allergy and intolerance, to address identified policy needs.

The Programme was originally set up in 1994 by the Ministry of Agriculture Fisheries and Food (MAFF), with the primary aim of investigating the causes and mechanisms of severe food allergy, in order to reduce its incidence and severity. At that time the Programme focused on the characterisation of peanut and tree nut allergies and on the later stages of food allergic disease when sensitisation has already occurred and developed into clinical allergy. Since then the Research Programme (T07) has evolved and, in line with the recommendations for research made by the 1998 Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment report on peanut allergy (http://cot.food.gov.uk/cotreports/cotwgreports/cotpeanutallergy) and the COT report on Adverse reactions to Food and Food Ingredients published in July 2000 (http://www.food.gov.uk/science/ouradvisors/toxicity/cotreports/cotwgreports/foodreactions), has widened and shifted its focus into epidemiology, mechanistic research and an increased amount of clinically based research. In particular, the focus of the Programme has developed to embrace investigations of the prevalence of food allergies and to try and establish whether, and to what extent, the prevalence of food allergy is increasing, particularly in childhood when many food allergies tend to develop.

In addition, the T07 Programme has also sought to identify factors (both genetic and environmental/dietary) that might influence the development of sensitisation to food allergens

[3] http://www.food.gov.uk/multimedia/pdfs/strategicplan2010e.pdf

(including the importance of timing, route and dose of exposure), in order to identify those at risk of developing food allergy and to inform future preventative strategies. The Programme has also funded research on thresholds of reactivity to gluten in coeliac disease to inform policy development on the definition of foods labelled as 'gluten-free'. Finally, the T07 Programme has also invested in investigations designed to explore a possible link between consumption of certain food additives and hyperactive behaviour in children. Most recently, the Programme has been focusing on how the early life environment, and in particular dietary and non-dietary exposures to allergenic foods, might influence or promote the acquisition of tolerance to allergenic foods (i.e. the ability to eat the allergenic food without ill effect), and to elucidate the associated underlying mechanisms.

Through the research that has been commissioned, the Programme aims to improve scientific understanding in food allergy and food intolerance. The results of the research are used to underpin the Agency's policy development, so that appropriate information can be used in risk management and communication by informing food allergic and food intolerant consumers to ensure their safety, and to inform their food choices. Further information on individual T07 projects can be found at:
http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/

3.4 Aims of the T07 Programme

The aims of the T07 Programme are laid out in the so-called 'ROAME' (Rationale, Objectives, Appraisal, Monitoring, Evaluation) document, which is a document used by the Agency to set out the strategic rationale, objectives and remit of its Research Programmes, and to underpin effective programme management and monitoring. In 2006 this document was replaced by an amended support document for Agency Research and Survey Programmes (RCU-B2 document). An extract from the ROAME for T07 for 2003 and from the T07 RCU-B2 document, which was agreed in July 2007, can be found at Annex 1 and 2. The aims of the Programme since July 2007 are:

- To identify the risk factors (e.g. genetic, environmental, dietary and other) associated with the development of sensitisation to food proteins and the development of clinical food allergy, particularly in early life. Knowledge of these factors and how they influence the development of sensitisation and allergy will enable us to develop appropriate advice for consumers to reduce the risk of development of food allergy.
- To investigate the immunological mechanisms of food allergy to understand, at the immunological level, what factors are important in determining/regulating the allergic versus tolerant status.
- To determine the prevalence of food allergy (both total food allergy and the prevalence of allergy to specific foods) in the UK in infants, children and adults, and whether prevalence is changing over time.
- To determine whether there is any association between exposure to certain food additives and behaviours in children.
- To develop suitable methods for the detection of allergens in food.
- To determine what factors influence the severity of allergic reactions to food.

4. The T07 Programme Review

4.1 Background to the Programme Review

To evaluate the success and productivity of the research that is commissioned, the Agency reviews individual Programmes of research every 5 years. The T07 Research Programme was last reviewed in November 2003 (in York), at which time all projects in the Programme active in the 5 year period from 1998 to 2003 were reviewed by a Panel of independent scientific experts[4]. The expert Review Panel and the Programme Advisor (Professor Ian Kimber) suggested areas for future research. These recommendations were taken into consideration in planning research calls issued since 2003, along with newly emerging policy needs, which have resulted in projects in a number of areas outside of these recommendations also being commissioned.

Since many of the projects commissioned since 2003 have now been completed or are a significant way through their life, it was considered both timely and appropriate to review the Programme formally again. The overall purpose of the present review was to evaluate the productivity, performance and relevance of the Programme against its aims and objectives (as set out on page 6) and against the outcomes of the previous Review and policy needs that have arisen since that time. In addition, the Review considered the future direction of the Programme and sought to identify, in conjunction with stakeholders, possible priority areas for Agency T07 funding for the next 5 years.

4.2 The Programme Review Meeting

The Review meeting was held in the Castle Hotel in Windsor from the 19th – 21st February 2008. The first 2 days of the meeting were an open meeting consisting of presentations and discussions on T07 projects, grouped according to subject area themes. In excess of 70 participants attended the open meeting, including representatives from academia, industry, research funding organisations, consumer organisations, research contractors and Government officials (see Annex 3 and 4 for a list of attendees from both the open and closed meetings). Some of these participants were specifically invited because of their expertise or interests in food allergy and intolerance research or policy. Other participants were those who had requested a place via an open invitation (which was placed on the Agency's website). The third day of the meeting was a closed session for the expert Review Panel, Agency officials and the T07 Programme Advisor, in which projects within the T07 Programme and the Programme as a whole were reviewed and recommendations made.

Projects were presented and reviewed in thematic groups to indicate the policy context of the research and to show, (where relevant), how projects were linked. There were 7

[4] http://www.food.gov.uk/multimedia/pdfs/t07review.pdf

different themes, with a total of 18 projects being presented over the course of the first and second day of the Review. There were opportunities for questions and discussion after each presentation as well as at the end of each theme and in addition there was also a separate Horizon Scanning session at the end of Day 2, which allowed all those in attendance to put forward and discuss possible future areas of research for the Programme to address. The Programme for the Review meeting can be found at Annex 5.

4.3 The Review Panel and Process

The expert independent Review Panel was appointed by the Agency and consisted of 6 scientific experts (including the Panel Chair) with, collectively, expertise in the fields of clinical allergy, paediatrics, immunology, nutrition, biochemistry and food science. The biographies of the Panel members can be found at Annex 6, and details of who was present at the closed session of the Review are in Annex 4. Panel members were assigned specific projects relevant to their area(s) of expertise and asked to assess these in detail prior to the Review meeting with respect to scientific quality and delivery. For each of these projects, the reviewers were provided with the relevant research call under which the work was originally commissioned, the original research proposal, scope of work (including any amendments) and pricing schedule(s). In addition, and where relevant, interim and final reports were provided, as well as any other relevant information on the progress and delivery of the projects. The reviewers' provisional assessments were submitted to the Agency in advance of the meeting. As individual projects to be reviewed were at very different stages of their life cycle, with some not yet yielding any results and others completed, it was inappropriate to assess all projects using exactly the same criteria. Therefore, reviewers were provided with 2 forms with which to complete their assessments, one for completed projects, and the other for ongoing projects.

Following presentations during the first 2 days of the meeting, reviewers had the opportunity to ask questions of clarification and to revise their comments and project evaluations accordingly.

In addition to the reviewers' comments, the Agency assessed each project against its relevance to Agency policy. These assessments, together with those of the reviewers, were considered and discussed during the closed meeting on the third day chaired by the Review Panel Chair, Professor Peter Aggett, then Head of School at Lancashire School of Health and Postgraduate Medicine. During these sessions individual projects were discussed and evaluated by the Panel as a whole. All provisional project scores and comments, along with any further relevant information deriving from the first 2 days of the meeting were taken into consideration, before the provisional scores were finalised. It should be noted that although Agency officials were present, this was primarily to observe proceedings and to provide clarification or context to the projects where invited to do so by the Panel.

The project evaluations were followed by a Panel discussion on the scientific quality and productivity of the Programme as a whole, taking into consideration the scores and comments of all the projects involved and how the Programme has performed against the aims and objectives that were set in 2003 and 2007 and against Agency policy needs. There was also a separate Horizon Scanning session at the end of day 3, where the Review Panel was invited to consider whether further research was needed in any of the themed areas covered by current or past projects. This enabled the Panel to suggest possible future areas of research for the Programme in other areas of relevance to the Agency's interests in food allergy and intolerance.

A summary of the discussions and conclusions of the Panel can be found in section 5.

4.4 Projects reviewed as Part of the T07 Programme Review

A total of 18 projects, in seven themed subject areas were reviewed. These projects are summarised below, with more detailed summaries available in Annex 7. A list of publications arising from each project as of February 2008 can be found in Annex 8.

Summary details of projects reviewed at the T07 Food Allergy and Intolerance Research Programme Review

Theme – Coeliac Disease				
Project Code	Project Title	Organisation	Lead Contractor	Project Duration
T07048	Systematic review on tolerable levels of gluten for people medically diagnosed with coeliac disease	Coeliac UK	Mrs Norma McGough	February 2006 - September 2006

Theme – Kiwi Allergy				
Project Code	Project Title	Organisation	Lead Contractor	Project Duration
T07025	Factors influencing the susceptibility to, and characteristics of, kiwi fruit allergy	University of Southampton	Dr Jane Lucas	April 2001 - September 2003
T07038	The characteristics of kiwi fruit allergy	University of Southampton	Dr Jane Lucas	January 2003 - December 2005

Theme – Consumer Information Research				
Project Code	Project Title	Organisation	Lead Contractor	Project Duration
T07045	Qualitative research into the information needs of teenagers with food allergy and intolerance	COI Communications	Ms Celia Watts	January 2005 - May 2005

Theme – Effects of Artificial Colourings and Preservatives on Behaviour in Children				
Project Code	Project Title	Organisation	Lead Contractor	Project Duration
T07040	Chronic and acute effects of artificial colourings and preservatives on children's behaviour	University of Southampton	Prof Jim Stevenson	September 2004 - February 2007 (main project), February 2008 (acute challenge)

Theme – Prevalence of Food Allergy and Intolerance				
Project Code	Project Title	Organisation	Lead Contractor	Project Duration
T07023	Prevalence and incidence of food allergies and food intolerance - a prospective cohort study to establish the incidence and a concurrent cross-sectional study of whole population cohorts at 1,2,3,6,11 and 15 years	Isle of Wight Healthcare NHS Trust	Prof Tara Dean	July 2001 - September 2006
T07034	An investigation into trends of peanut allergy incidence in the last 15 years in England using sequential childhood cohorts	Portsmouth University	Prof Tara Dean	April 2003 - March 2006
T07035	The prevalence of peanut allergy in British children at school entry age in 2003	University of Southampton	Prof Jonathan Hourihane	April 2003 - August 2005
T07046	The prevalence of food allergy and weaning practices in a birth cohort of UK infants	University of Southampton	Dr Graham Roberts	August 2005 - October 2009

Theme – Immunological Aspects of Food Allergy				
Project Code	Project Title	Organisation	Lead Contractor	Project Duration
T07041	The role of peanut-specific T cell responses in children with peanut allergy and in children who are tolerant to peanuts	King's College London	Prof Gideon Lack	April 2004 - March 2008
T07042	Longitudinal study of T cell responses in development and resolution of food allergy	University of Cambridge	Prof Pam Ewan	July 2004 - January 2010
T07032	The role of IgG in allergy and tolerance to common food allergens	University of Cambridge	Prof Pam Ewan	September 2003 - August 2006
T07033	The Immunomodulatory role of maternal IgG in infant atopic programming	University of Southampton	Prof John Warner	May 2003 - August 2005

Theme – Importance of Route and Timing of Exposure to Allergens Including Maternal Factors				
Project Code	Project Title	Organisation	Lead Contractor	Project Duration
T07044	Peri-natal egg and milk allergen exposure in relation to tolerance or allergic sensitisation to food in infancy	University of Southampton	Prof John Warner	April 2004 - December 2006
T07026	To investigate the influence of maternal experience of dietary antigen on the subsequent immune status of their offspring	University of Bristol	Dr Bevis Miller	March 2002 - August 2006
T07043	Peanut allergy: routes of pre-natal and post-natal exposure	King's College London	Prof Gideon Lack	September 2004 - September 2005
T07049	Characterisation of the immune mechanisms involved in the induction of oral tolerance to peanuts in children	King's College London	Prof Gideon Lack	July 2007 - July 2012
T07051	Randomized controlled trial of early introduction of allergenic foods to induce tolerance in infants	King's College London	Prof Gideon Lack	January 2008 - July 2014

5. Findings of the Review

The following sections summarise the consensus views of the Review Panel on the research funded under the T07 Programme since 2003. Whilst projects were evaluated individually it is not the purpose of this document to detail the evaluations, which have been fed back to the contractors where relevant.

5.1 Scientific Quality and Productivity of the Programme

The Review Panel considered that the quality of the science within the portfolio of projects that currently make up the T07 Programme was generally of a very high standard. The Panel also considered that the Research Programme as a whole had been very productive when considering the number of projects funded, their success in delivering against their aims and objectives, and given the relatively small size of the T07 Programme budget. The high scientific quality and rigour of projects in several of the themed areas were specifically commented on and discussed, in particular projects which had sought to determine the prevalence of food allergies, certain aspects of the work the Agency had funded on kiwi allergy, and on investigation of the possible importance of non-oral routes of exposure in the acquisition of sensitisation to peanut.

The Panel considered that having access to the right balance and breadth of scientific expertise within the research teams was of critical importance for delivering high quality science, particularly where projects were covering several different areas of science and that this is an aspect that should be strengthened in the future. It was recommended that the Agency seek to ensure that research teams have the right balance of expertise, or have access to it via collaboration, at the outset of new T07 projects where multiple subject areas are involved, in order to maintain high scientific quality and success of projects.

5.2 Delivery Against T07 Aims and Objectives

The consensus from the Panel was that the Research Programme had been very successful in addressing the majority of its aims as set out in the Programme support document (Annex 2). The Panel considered that collectively the projects funded within the Programme over the last 5 years have significantly moved forward the state of current scientific knowledge in a number of these areas (see more detailed comments below). The Panel recognised that the objectives within the 2007 T07 Programme support document (Annex 2) were only finalised within the last year and therefore reflect how the Programme will evolve over the next 5 years, rather than what has already been achieved.

The Panel agreed that the T07 Programme had made significant progress in identifying risk factors associated with the development of sensitisation and food allergy, via projects which have highlighted the importance of timing, route and dose of exposure and those which have established the skin as potentially a very significant route of sensitisation to

food proteins. However, it was considered that there is still scope for further research in this area and it was recognised that the Agency does already have a number of projects in place. The Panel considered that these should provide further and more definitive information about the precise influence of early life dietary and non dietary exposures on immunological outcome (these include projects T07046, T07049, and T07051).

The Panel suggested that it would be useful for the UK to develop a severe reactions register to record food allergic reactions in order to help identify further risk factors for allergic reactions. Some EU countries already have such registers in place. However, it was recognised that this would require careful thought, would probably need to be centrally resourced and managed, and would need to be designed appropriately to capture all of the relevant information. It may also not be within the Agency's remit to put in place such a register.

The Panel noted that the Programme had also conducted a number of pieces of research to establish the prevalence of food allergy in children of different ages and to study the epidemiology of food allergic disease. It was recognised that these studies are difficult to undertake, and required very large numbers of subjects because of the relatively low prevalence of these conditions. The Panel considered that this work had been conducted well and had provided the Agency with robust data on the prevalence of food allergies at different ages and about the natural history of individual food allergies during childhood. The results were considered to be very relevant to Agency policy. It was suggested that perhaps some of the work could have been replicated in older cohorts, as there are few data currently available on the prevalence of food allergies among UK adults or for different population sub-groups.

The Panel discussed the research that the Programme had funded on the immunological mechanisms of food allergy. It was agreed that a number of the projects in the T07 Programme had begun to move forward the understanding of what immunological factors are (and are not) important in determining/regulating sensitisation, clinical allergy and tolerance to food proteins. The Panel thought that this work had been conducted well, although some of it was descriptive rather than mechanistic in nature and could benefit from greater use of immunological assays, based on function rather than amount of particular markers. It was recognised that further research needs to be conducted in this area in order to underpin possible future preventative/treatment strategies for food allergy. It was recommended that the Agency consult with expert mechanistic immunologists before commissioning any further research, to ensure that the work proposed is relevant, based on the latest techniques in immunology and has the greatest potential to have a significant impact on the scientific community and the state of current knowledge.

The Panel considered that the T07 Programme had funded an important and very difficult piece of research investigating whether there was an association between exposure to certain mixtures of food additives and behaviour in children, and that this research was of

high scientific quality. The Panel noted that the results of the research had been complex and not straightforward to interpret, and that they had been the subject of in depth evaluation and peer-review, via the Committee on Toxicity (COT) and the European Food Safety Authority (EFSA). The Panel also noted that the project outcomes had directly informed Agency policy, leading to the issue of new precautionary advice to parents and consideration of the issue at European level. It was considered that any future research in this subject area would probably fall within the remit of other funding agencies/departments rather than the T07 Programme, depending on the specific questions the research was seeking to address and the instruments and outcomes that would be needed.

One aim of the Programme which the Panel considered had not been addressed to any significant degree was the area of developing methods for the detection and quantification of allergens in foods. Whilst 1 project in this area had been funded previously by the Programme, no further projects in this area had been commissioned since then. The Panel suggested that the Programme gives further consideration to development of reliable methods which can accurately quantify the amount of an allergen in foods. In addition there is a need for development of established reference materials for the major allergenic foods against which to calibrate the methods. Although there are currently both protein and DNA methods for certain allergens, there is a need to improve the protein methods available and to validate these independently to ensure they are robust and fit for purpose. Alongside these requirements, the Panel noted that there is a strong need for further information on thresholds of reactivity, to food allergens, from which regulatory thresholds which would be adequately protective at a public health level could be developed. Such regulatory thresholds would assist enforcement officers and the food industry, as well as regulators themselves, in risk assessment and risk management activities.

Although the Panel agreed that there is a requirement for further research in the areas of methods and thresholds, it was acknowledged it would be the collective responsibility of a number of bodies, both national and international, including relevant government departments, Research Councils, industry, other EU Member States and food authorities to take this work forward. It was recognised that an approach harmonised at EU or wider level would be preferable, for developing new methods for detecting allergens in food, understanding the spectrum of sensitivity in allergic individuals and populations, and using this to develop regulatory thresholds to inform labelling decisions. The Panel also considered that the factors which affect severity of allergy as a whole, including but not limited to food allergy, may need to be considered including importance of both intrinsic and extrinsic factors influencing severity.

5.3 Overall Conclusions of the Panel

The Panel agreed that the quality of the science within the Programme was of a high standard and that the Research Programme as a whole since 2003 had been valuable. The Panel commented that not only had the research generally been conducted well, but it had delivered a large number of outputs. These have been relevant to the Agency's policy and often the results have been translated into sound consumer advice. It was considered that the results of the projects funded by the Programme since 2003 had collectively made a significant contribution to the understanding of food allergy on both a national and international scale. It was considered that this was particularly impressive given the relatively small size of the T07 Programme budget.

5.4 Impact of the T07 Programme's Outputs on Agency Policy

The impact of the findings of individual completed projects on Agency policy (or for ongoing projects, the potential impact), was evaluated initially by Agency officials. The results of this were then discussed with and commented on by the Review Panel at the Review meeting.

The Programme has worked to address a number of policy needs, and has made significant impacts in a number of areas. This includes the research on food additives and children's behaviour, which directly informed Agency policy leading to the issue of new precautionary advice to parents and consideration of the scientific evidence base at a wider European level. The work the Programme has funded on the prevalence of food allergy and intolerance has established UK estimates for the prevalence of clinical allergy and sensitisation to foods for a wide range of food allergens in several age groups of children and teenagers for the first time, and has used robust methodologies for diagnosis of food allergy unlike many of the previous studies on prevalence. These data will provide a benchmark from which to evaluate future changes in prevalence with more scientific certainty than is currently possible. The research which has considered the impact of the 1998 Government advice on peanut consumption during pregnancy and weaning is likely to inform future Agency policy. The results of the literature review conducted for the Agency represents a significant part of the body of scientific evidence, that is currently being reviewed by the COT in reaching a decision on whether this advice remains appropriate, based on the current scientific thinking.

Research that the Programme had previously funded using animal models, coupled with the more recent clinical research in humans that it has funded on the possible importance of non-dietary routes of exposure, has drawn attention to the probable importance of the skin as a relevant and potentially significant route of exposure for the acquisition of sensitisation to peanut, and possibly other food proteins. These results, along with the results of further research being funded currently by the Programme to evaluate the

importance of early dietary exposure, may have significant implications for the development of future policy and advice to parents, to minimise the risk of their child developing food allergy.

The 2 projects on kiwi allergy have together represented the first study of kiwi allergy in the UK and the largest clinical study of the allergy worldwide. These projects characterised kiwi fruit allergy as a significant and rapidly growing cause of food allergy in the UK which can be severe, especially in children. Projects funded in this area have not only provided valuable data on the severity of kiwi allergy (especially in children), but also on how to diagnose kiwi allergy and on the allergenicity of gold kiwi in addition to green kiwi. The information gained from these pieces of research has directly informed the Agency's advice and led to a separate section on the Agency's website on kiwi allergy. It also informed the advice given by the Department of Health, to schools at the time of the introduction of the school fruit and vegetable scheme in 2004.

The T07 Programme also commissioned research into the role of IgG antibody in food allergy. 2 major conclusions can be drawn from this work, firstly is that differences in IgG antibody levels do not explain inter-individual differences in the severity of allergic reactions and secondly, that IgG antibody production is a normal immunological response to dietary exposure to food proteins and does not signal allergy or intolerance. The Agency is therefore now well-positioned to make it clear to members of the public that measurement of specific IgG antibody levels cannot be used as a reliable diagnostic of egg and peanut allergy and is also likely to be the same for other food allergies.

6. Suggestions for Future Research in the T07 Programme

The Programme Review meeting allowed all those in attendance to consider whether further research was needed in any of the themed subject areas covered. In addition, to consider and suggest possible future areas of research for the Programme outside of these existing themes.

In addition, during the closed session on the third day the review Panel also discussed a number of ideas for future research, taking into consideration the suggestions made during the Horizon Scanning session on the 2nd day. Within this the Review Panel emphasised the importance of continued support for the T07 Programme, especially considering the significant contribution to the understanding of food allergy that the Programme has made in the last 5 years and the likely impact the Programme will have in the next 5 years.

It should be noted that some of the areas which were suggested for future research and which are detailed below may fall outside the remit of the T07 Programme. However, they have nevertheless been included in this report for completeness and since they may inform research planning and prioritisation processes by other funders with an interest in food allergy.

6.1 Current Themes

The Panel first assessed the current T07 research themes and made recommendations to the Agency on whether any further research was needed in these areas.

Coeliac Disease

The Panel considered that further research could be warranted in this area both to progress scientific understanding and to further inform policies on safe threshold levels. It was recognised that, whilst the Programme had drawn together the published evidence on thresholds of reactivity to gluten and although a new International Standard setting maximum levels for gluten in 'gluten-free' foods has now been agreed. From a scientific viewpoint there is a still a need to determine the threshold level of gluten that will cause histological changes in the coeliac patient, including the dose response relationship. It was suggested that information was particularly needed on the amount (in mg) rather than the concentration in food causing symptoms, and that this then needs to be put in the context of exposure. It was also recognised that future research on coeliac disease could concentrate on a number of different areas including T-cell reactions to gluten and the use of functional assays to investigate how the food matrix affects the absorption of gluten.

Kiwi Allergy

The Panel acknowledged that projects funded in this area have provided the Agency with valuable data and evidence on which to base clear consumer advice and information about this allergy. It was considered by the Panel that further work should not be funded in this area at this time, although there could still be benefit in exchanging sera from kiwi allergic patients with researchers in other countries in order to compare the allergenic proteins.

Consumer Information Research

The Panel were extremely positive about the research that had already been conducted by the T07 Programme in this area, through which they considered much insight had been gained about the information needs of teenagers, and the particular challenges and risks that are presented by this important group of food allergic consumers. No specific recommendations regarding further research in this area were made by the Panel, but it was noted that emerging policy needs may influence the need to call for new research in this area and future considerations of risk communication with children.

Effects of Artificial Colourings and Preservatives on Behaviour in Children

The Panel considered that the T07 Programme had already funded a significant amount of research in this area, including 2 major studies of international importance, which had informed Agency policy. No specific recommendations were made by the Panel for further research in this area at this time, and it was noted that other funding bodies/departments (including those outside the UK) may be better placed to fund further studies in this area, if appropriate, in the future.

Prevalence of Food Allergy and Intolerance

The Panel recognised that the Programme had already commissioned a number of studies which have aimed to establish the prevalence and natural history of food allergies in children and teenagers. It was considered that future research could concentrate on determining the prevalence of food allergies in UK population sub-groups (such as ethnic migrant groups) and also in adults, as there are few data available on the prevalence of food allergy among these groups. However, it was recognised that these studies are difficult to conduct and would require larger cohorts than the studies in children, if robust data are to be acquired. The Panel also suggested that there could be merit in the future in following up existing cohorts to look at how food allergy evolves longitudinally.

Immunological Aspects of Food Allergy

The Panel thought it important that the T07 Programme to conduct further research on the immunological aspects of food allergy, especially as this could underpin possible future preventative/treatment strategies for food allergy especially given how little is still known about the underlying immunological mechanisms which determine and regulate

food allergic disease. The Panel suggested that the Agency should consider, where appropriate, consulting with expert mechanistic immunologists beyond the field of food allergy, to identify future specific areas of research within the overall subject area of the immunology of food allergy and to identify the key unanswered research questions. The Panel also recognised the importance of co-funding and where appropriate, taking a collaborative approach to funding, especially given that this subject area involves research that is fundamental rather than applied.

Importance of Route and Timing of Exposure to Food Allergens, Including Maternal Factors

The Panel acknowledged that the T07 Programme had made significant progress in identifying risk factors associated with the development of sensitisation and food allergy, and in identifying the possible importance of different routes of exposure in sensitisation, through recent and previous projects funded under the Programme. The Panel appreciated that since the Programme had recently commissioned 2 major projects on maternal/infant diet and timing of exposure to allergenic foods in the context of immunological outcomes, that no further research in this area should be commissioned until the existing projects are complete.

However, the Panel did suggest that additional research could be commissioned to establish the importance of non-dietary routes of exposure to allergenic foods on the acquisition of sensitisation and allergy, building on the findings of the previous studies it has funded in this area.

6.2 Other Areas of Work Outside the Current Themes and General Recommendations

The Panel also considered other areas of potential importance to the T07 Programme that are outside the current themes of work, and made several general recommendations regarding commissioning research in the future.

Relevant Expertise

The Panel recommended that the Agency should always ensure research teams have the right balance and breadth of scientific expertise, or have access to it via collaboration, at the outset of new projects in order to maintain high scientific quality and success, particularly where projects cover several different scientific areas. The Panel noted that this had not been the case for every project. It was also suggested that for smaller projects where steering groups are not always necessary, the research teams need to ensure they are communicating effectively and, if necessary, collaborating with the relevant experts in the field(s) in order to ensure high quality, robust and appropriate experimental methodologies are being used.

Collaboration

The Panel recommended that, where appropriate, the Agency seeks to collaborate with other relevant funding bodies when commissioning research on food allergy and intolerance in the future. It was suggested that not only is joint funding likely to represent better value for money for the Agency, but it may also give the Agency an opportunity to fund larger pieces of work which it may not be possible for it to fund alone.

Dissemination

The Panel made a general point about ensuring appropriate and extensive dissemination of the outcomes of T07 funded work. It was considered that a number of T07 projects had some very important results which would be of interest both to the scientific community and in some cases to non-scientific audiences such as food manufacturers or other specialist stakeholder groups. The Panel recognised that some projects within the Programme had been disseminated well, but it was recommended that all T07 funded work is published in a journal. Researchers and the Agency should take steps to ensure that the results are disseminated through a number of routes such as, conferences aimed at the wider scientific community, as well as proactively communicating messages via the media in magazines and website articles where appropriate, in order to reach a wider lay audience.

Novel Foods

The Panel suggested that the Agency should consider conducting post market monitoring on novel foods, although it was agreed that this may not fall within the remit of the T07 Programme.

Methods

The Panel considered that further research was required to improve and validate methods to detect and quantify allergens in foods, which would help to underpin enforcement, risk assessment and risk management activities by both industry and regulators. This could include validation studies of existing methods, development of new methods utilising other technologies and/or developing and making available reliable reference materials against which to calibrate methods.

Severity of Reaction

The Panel considered that further research should be commissioned to establish what determines the severity of food allergic reactions and to identify and characterise the role of extrinsic and intrinsic factors that may affect the severity of reaction, including the food matrix. It was noted that research in this area could inform policy in a number of areas, including the development of labelling thresholds for allergenic foods, targeted advice to consumers and could also inform work on analytical methods.

However, the Panel did note that the factors which effect severity of allergy as a whole rather than just food allergy may need to be considered. The Panel suggested that it may be appropriate to collaborate with other funding bodies in this context.

Food Intolerance

The Panel considered that much of the current T07 research concentrates on food allergy and yet very little is known about food intolerance. Further research could be funded on food intolerance in a number of areas, including studies to characterise the disorders and to establish prevalence. However, it was recognised that other than for coeliac disease, reliable diagnostic criteria are often not available and so research may need to start in this area.

Register of Food Allergic Reactions

The Panel suggested that it would be extremely useful for the UK to develop a severe reactions register to record food allergic reactions, in order to collate prospectively, information about severe reactions as they occur, at a regional or national level, and to help identify further risk factors for reactions. It was considered that this would be a particularly useful tool for clinicians and the Agency for a number of purposes. However, it was recognised that this would require careful thought. It would probably not be within the remit of the Agency to set this up, would need to be centrally resourced and managed, and be of an appropriate design to capture all of the relevant information.

Public Perception of Risk Assessment

The Panel also suggested that further research could be conducted on the public perception of risk in the context of allergens in food, which would inform development of risk assessment and risk management strategies.

7. Conclusions and Way Forward

The Agency's work on food allergy and intolerance aims to protect food allergic and food intolerant consumers and to help them to make informed choices about food. The outputs of research funded by the T07 Research Programme over the last 5 years have collectively served to improve the advice given by the Agency to consumers with food allergies, in several different areas, as outlined above. The Programme has also made significant contributions to moving forward the state of scientific knowledge in several key areas including prevalence, mechanistic research, new food allergies, food additives and behaviour in children and on the importance of route and timing of exposure in the development of food allergy.

In moving forward into the next 5 years of the Programme's life, the Agency will seek to reflect on the valuable comments and recommendations that have been made by the Review Panel about the performance, productivity and scientific quality of the Programme, with the hope of improving the Programme even further in the future.

With regard to the suggested areas for future research, these have been considered carefully by the Agency in formulating a plan of the way forward, based on consideration of the suggested areas against a number of different factors and criteria. As part of this process, all ideas put forward during both Horizon Scanning sessions at the Review meeting, have been considered by the Agency against the remit of the Programme and of the wider Agency, the strength of the policy need, feasibility and the available budget. Our knowledge of the research that is already being undertaken by other organisations or funding bodies on food allergy and intolerance was also taken into account.

The result of these considerations is that a number of different areas were considered to be of particular importance, as listed below. It is important to note that this is not an exhaustive or exclusive list of the activities/funding areas of the Programme for the next 5 years, but rather a list of those areas which have been identified as being of particular importance for us to address in the short to medium term. Developments in our scientific knowledge and/or changing or new policy needs may well emerge which will influence the Agency's decisions about specific areas in which to call for research and at what time in the future.

Areas of Focus for the T07 Programme for the Next 5 Years.

- Commission further research on the importance of environmental (including dermal) exposure to allergenic foods as a route of sensitisation, building on previous Agency funded research in this area.
- Commission research to underpin work on deriving management thresholds for allergenic foods.
- Engage with other stakeholder activities both nationally and internationally as appropriate and consider commissioning research to improve the reliability of methodologies for the detection and quantification of food allergens in food products.
- Host a scientific workshop to identify and prioritise what further basic immunology work needs to be conducted on food allergy, and issue future research calls in this area as appropriate.

Annex 1

RCU-B2 – Aims and Objectives of the Food Allergy and Intolerance Research Programme (T07)

(JULY 2007)
RCU-B2

Support Document for Research/Survey Programmes

Section 1 – General

Budget Holder	MICHAEL WIGHT	For Business Planning 2007-08
Policy division	LABELLING, STANDARDS AND ALLERGY DIVISION (LSA)	
Programme title	FOOD ALLERGY AND INTOLERANCE RESEARCH PROGRAMME (T07)	
Programme Manager	JOELLE BUCK	

Summary of the rationale for the Programme

The overarching aim of this Research Programme is to provide robust scientific evidence to underpin the development of sound and evidenced based policies and advice on food allergy and intolerance. This assists us in achieving our stated aims of ensuring the safety of food allergic and intolerant consumers and helping them to make informed choices.

In the UK at least 10 people are known to die every year from an allergic reaction to food, although the true figure is thought to be higher. Many more end up in hospital. This is in addition to the longer term health effects and impact on quality of life which those experiencing these conditions face. Current estimates suggest that approximately 2 adults in every 100 (and up to 5 in every 100 children) have been diagnosed with a food allergy, with an

additional 1 person in 100 being intolerant to gluten. These together equate to a total of 1.8 million people in the UK. In addition, it is estimated that 1 in 70 children have peanut allergy.

The overall aim of the Agency's work on food allergy and intolerance is to protect food allergic and food intolerant consumers and to help them to make informed choices about food. The Agency achieves the above aim through negotiating and implementing legislation to improve statutory control on labelling of food allergens, and also by providing best practice guidance for industry and enforcement bodies to encourage greater awareness and control of food allergens through the food supply chain. In addition, the Agency provides advice about food allergy and intolerance for consumers, to help them make informed food choices and to ensure their safety.

The main focus of the Programme is on investigating the causes and mechanisms of food allergy, particularly severe food allergy, in order to reduce the incidence and severity of this disease. The Programme also seeks to conduct research on those food intolerances where there is a known or hypothesised immunological component (for example coeliac disease). Research on non-allergic adverse reactions to foods which are not thought to involve the immune system in any way, for example toxicological or pharmacological reactions to foods, or other foods sensitivities with miscellaneous causes, are generally outside the scope of this Research Programme. However, within the remit is consideration of whether there exists a relationship between dietary exposure and adverse effects on the behaviour of children; effects that are not normally believed to be allergic in nature.

Within the context of the overall aims stated above, the Programme seeks to address the following research objectives:

- To identify the risk factors (e.g. genetic, environmental, dietary and other risk factors) associated with the development of sensitisation to food proteins and the development of clinical food allergy, particularly in the early life stages of the individual. Knowledge of these factors and how they influence the development of sensitisation and allergy will enable us to develop appropriate advice for consumers to reduce the risk of development of food allergy.
- To investigate the immunological mechanisms of food allergy to understand, at the immunological level, what factors are important in determining/regulating the allergic versus tolerant status.
- To determine the prevalence of food allergy (both total food allergy and the prevalence of allergy to individual foods) in the UK in infants, children and adults, and whether prevalence is changing over time.
- To develop the best research approach and methods to investigate whether there is any association between intolerance to certain foods and children's behaviour.
- To develop suitable methods for the detection of allergens in food.
- To determine what factors influence the severity of allergic reactions to foods.

Annex 2

Extract from T07 ROAME Document (2003)

Previous aims and objectives of the Food Allergy and Intolerance Programme

Updated November 2003

To investigate the cause and mechanisms of severe food allergy, with emphasis on peanut allergy, in order to reduce the incidence and severity.

The research will contribute to the Agency's strategic aims on the chemical safety of food and food products, public information, labelling and choice, building consumer confidence and taking in the needs of disadvantaged groups.

The number of individuals suffering from allergic reactions to food appears to be increasing in line with a general increase in allergy in the UK, such as asthma and eczema. As many as 1 in 200 UK children may now react to peanuts; indeed, peanut allergy is the most common cause of severe (fatal and near fatal) allergic reactions to foods, causing 30% of all cases of anaphylaxis outside the hospital. The Food Standards Agency funds research in order to continue to reduce the incidence and severity of food allergy and food intolerance.

The research has mainly focused on characterisation of peanut and treenut allergens, and work is underway to look at the differences in the reactivity of allergic individuals to treenuts and peanuts. Much of the research in this area has concentrated on the later stages of the disease, when allergy has already developed. Studies have indicated that the majority of peanut allergic individuals react to their first known exposure to peanut. This suggests unsuspected prior sensitisation and so work is being funded to examine the role of maternal and weaning diets in initiation of allergic disease. A report of a sub-group of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) published in 1998, recommended further investigation of the routes of sensitisation of peanut allergy.

More recently, studies have been funded to establish to what extent the prevalence of food allergy is increasing. Studies are also being funded on methods of identifying those at risk of developing food allergy in line with recommendations made by the COT report on Adverse Reactions to Food and Food Ingredients published in July 2000.

There is a need to develop easy and reliable tests to identify allergens in food: research investigating a molecular-based test is underway.

This Programme of research will provide information about the fundamental basis of factors that influence the development of food allergy. This will help consumers by:

- Identifying risk factors associated with the development of food allergy so that information can be given to consumers to take preventive measures.
- Determining the prevalence of food allergy and whether this is changing with time.
- Developing methods for the detection of allergens in food.

Annex 3

List of Participants for Day 1 and 2 of the Review Meeting

Professor Peter Aggett	Panel Chairman	University of Central Lancashire
Joshua Atkinson		Food Standards Agency
Dr Kirsten Beyer		Europrevall
Professor Jonathan Brostoff		King's College, London
Dr Helen Brown		Campden and Chorleywood Food Research Association
Dr Joelle Buck		Food Standards Agency
Professor Judy Buttriss	Panel Member	British Nutrition Foundation
Dr Susan Chan		King's College, London
Dr Andrew Clark		University of Cambridge
Dr René Crevel		Unilever, ILSI
Dr Andy Damant		Food Standards Agency
Dionne Davey		Food Standards Agency
Professor Tara Dean		Isle of Wight Healthcare NHS Trust
John Deighton		University of Cambridge
Professor Stephen Durham		Imperial College, London
Professor Christine Edwards		University of Glasgow
Professor Pamela Ewan		University of Cambridge
Dr Chris Exley		Keele University
Gill Fine		Food Standards Agency
Katherine Fleming		
Dr Adam Fox		King's College, London
Professor Anthony Frew	Panel Member	Brighton Medical School
Professor Paul Garside	Panel Member	University of Strathclyde
Hazel Gowland		Allergy Action
Kate Grimshaw		University of Southampton
Phil Goodwin		Hallmark Analytical Ventures
Sarah Hardy		Food Standards Agency
Sue Hattersley		Food Standards Agency
Dr Karin Haverson		University of Bristol

Frances Hill		Food Standards Agency
Dr Chris Hodge		CRH Associates
Ruth Hodgson		Food Standards Agency
Professor Jonathan Hourihane		University College Cork
Dr Sabita Islam		University of Cambridge
Elizabeth Kendall		Food Standards Agency
Professor Ian Kimber	Programme Advisor	University of Manchester
Sr Yvonne King		University of Cambridge
Professor Gideon Lack		King's College, London
Dr Jane Lucas		University of Southampton
Dr Ingrid Malmheden Yman	Panel Member	National Food Administration, Uppsala
Kate May		Food Standards Agency
Professor Tom McDonald		Medical Research Council
Norma McGough		Coeliac UK
Dr Bevis Miller		University of Bristol
Dr Clare Mills	Panel Member	Institute of Food Research, Norwich
Emma Peacock		Food Standards Agency
Dr Michael Perkin		King's College, London
Dr Bert Pöpping		Eurofins
David Reading		Anaphylaxis Campaign
Dr Graham Roberts		University of Southampton
Maureen Jenkins		Allergy UK
Professor Jim Stevenson		University of Southampton
Dr Caroline Tahourdin		Food Standards Agency
Dr Victor Turcanu		King's College, London
Dr Carina Venter		Isle of Wight Healthcare NHS Trust
Dr Andrew Wadge		Food Standards Agency
Dr Michael Walker		Laboratory of Government Chemists
Professor John Warner		Imperial College, London
Dr Ursula Wells		Department of Health
Michael Wight		Food Standards Agency
Dr Paul Willets		Food Standards Agency
Dr Liz Williams		Nutrition Society
Jill Wykes		RHM Technology, Premier Foods

Annex 4

Closed Session Attendees (Day 3)

The Review Panel compromised of 6 independent experts with relevant experience in immunology and nutrition.

Chairman

Professor P Aggett	Lancashire School of Health and Postgraduate Medicine, University of Central Lancashire

External Reviewers

Professor J Buttriss	British Nutrition Foundation (BNF)
Dr C Mills	Institute of Food Research, Norwich
Dr I M Yman	National Food Administration, Uppsala
Professor P Garside	University of Strathclyde
Professor A Frew	Brighton Medical School

Programme Advisor

Professor Ian Kimber	University of Manchester

FSA Officials

Mrs Sue Hattersley	Food Allergy Branch
Dr Joelle Buck	Food Allergy Branch
Miss Sarah Hardy	Food Allergy Branch
Miss Ruth Hodgson	Food Allergy Branch
Miss Elizabeth Kendall	Food Allergy Branch
Dr Paul Willetts	Chief Scientist Team
Mr Joshua Atkinson	Statistics Advice Unit
Mrs Kate May	Novel Foods, Additives & Supplements Branch

Annex 5

FSA T07 Food Allergy & Intolerance Research Programme Review

Windsor 19–20 February 2008

PROGRAMME OF EVENTS

Please note that the current affiliation of the presenter for each project has been given in the programme of events. In some cases this is different from where the work was conducted.

Tuesday 19 February 2008

Day One: Registration and introduction

2.00 – 3.00	Registration and refreshments	
3.00 – 3.15	Welcome and introduction to FSA strategic aims and policy needs on food allergy and intolerance	Mrs Sue Hattersley *(Food Standards Agency)*
3.15 – 3.20	Questions	
3.20 – 3.35	Establishment and evolution of the food allergy T07 Research Programme	Professor Ian Kimber *(Programme Advisor)*
3.35 – 3.40	Questions	

Day One: Presentations on Themes of Research

Session One Research Theme: Coeliac Disease

Chair – Professor Ian Kimber

3.40 – 3.45	Introduction to research theme	Professor Ian Kimber *(Programme Advisor)*
3.45 – 4.00	T07048 - Coeliac disease and gluten thresholds	Mrs Norma McGough *(Coeliac UK)*
4.00 – 4.10	Questions	

Session Two **Research Theme: Kiwi Allergy**

Chair – Professor Ian Kimber

4.10 – 4.15	Introduction to research theme	Professor Ian Kimber *(Programme Advisor)*
4.15 – 4.35	T07025 – Factors influencing the susceptibility to, and characteristics of kiwi allergy	Dr Jane Lucas *(University of Southampton)*
	T07038 – The characteristics of kiwi fruit allergy	Dr Jane Lucas *(University of Southampton)*
4.35 – 4.50	Questions	
4.50 – 5.00	Tea and coffee break	

Session Three **Research Theme: Consumer Information Research**

Chair – Professor Ian Kimber

5.00 – 5.05	Introduction to research theme	Mrs Sue Hattersley *(Food Standards Agency)*
5.05 – 5.15	T07045 - Qualitative research into the information needs of teenagers with food allergy and intolerance	Mrs Sue Hattersley *(Food Standards Agency)*
5.15 – 5.25	Questions	

Session Four **Research Theme: Effects of Artificial Colourings and Preservatives on Behaviour in Children**

Chair – Mrs Sue Hattersley

5.25 – 5.35	Introduction to research theme	Professor Ian Kimber *(Programme Advisor)*
5.35 – 6.05	T07040 - Effects of artificial colourings and preservatives on children's behaviour	Professor Jim Stevenson *(University of Southampton)*
6.05 – 6.20	Questions	
8.00	Dinner for all participants	

Wednesday 20 February 2008

Day Two: Presentations on Themes of Research

Session Five **Research Theme: Prevalence of Food Allergy**

Chair – Professor Ian Kimber

8.30 – 8.35	Introduction to research theme	Professor Ian Kimber *(Programme Advisor)*
8.35 – 9.05	T07023 - Prevalence and incidence of food allergies and food intolerance- a prospective cohort study to establish the incidence and a concurrent cross-sectional study of whole population cohorts at 1,2,3,6,11 and 15 years	Dr Carina Venter *(St Mary's Hospital, Isle of Wight)*
	T07034 – An investigation into trends of peanut allergy incidence in the last 15 years in England using sequential childhood cohorts	Professor Tara Dean *(St Mary's Hospital, Isle of Wight)*
9.05 – 9.20	Questions	
9.20 – 9.40	T07035 – The prevalence of peanut allergy in British children at school entry age in 2003	Professor Jonathan Hourihane *(Cork University Hospital)*
9.40 – 9.55	Questions	
9.55 – 10.00	T07052 – Systematic literature review on early life peanut avoidance/exposure and development of later allergy	Dr Joelle Buck *(Food Standards Agency)*
10.00 – 10.20	T07046 – The prevalence of food allergy and weaning practices in a birth cohort of UK infants	Dr Graham Roberts *(University of Southampton)*
10.20 – 10.35	Questions	
10.35 – 10.50	Tea and coffee break	

Session Six **Research Theme: Immunological Aspects of Food Allergy**

Chair – Professor Ian Kimber

10.50 – 10.55	Introduction to research theme	Professor Ian Kimber *(Programme Advisor)*
10.55 – 11.15	T07041 – The role of peanut specific T cell responses in children with peanut allergy and in children who are tolerant to peanuts	Dr Victor Turcanu *(King's College, London)*
11.15 – 11.30	Questions	
11.30 – 12.00	T07032 – The role of IgG in allergy and tolerance to common food allergens	Dr Andrew Clark *(University of Cambridge)*
	T07042 – Longitudinal study of T cell responses in development and resolution of food allergy	Dr Andrew Clark *(University of Cambridge)*
12.00 – 12.15	Questions	
12.15 – 12.40	T07033 – The immunomodulatory role of maternal IgG in infant atopic programming	Professor John Warner *(Imperial College, London)*
	T07044 – Peri-natal egg and milk allergen exposure in relation to tolerance of allergic sensitisation to food in infancy including a brief history of previous linked Agency-funded projects	
12.40 – 12.55	Questions	
12.55 – 1.55	Lunch	

Session Seven **Research Theme: Importance of Route and Timing of Exposure to Food Allergens Including Maternal Factors**

Chair – Mrs Sue Hattersley

1.55 – 2.00	Introduction to research theme (including T07044)	Professor Ian Kimber *(Programme Advisor)*

2.00 – 2.15	T07026 – Investigation of the role of maternal experience of dietary antigen on the subsequent immune status of their offspring	Professor Bevis Miller *(University of Bristol)*
2.15 – 2.30	Questions	
2.30 – 2.45	T07043 – Peanut allergy: routes of pre-natal and post-natal exposure	Dr Adam Fox *(King's College, London)*
2.45 – 3.00	Questions	
3.00 – 3.15	T07049 – Peanut intervention study	Professor Gideon Lack *(King's College, London)*
3.15 – 3.30	Questions	
3.30 – 3.45	T07051 – Randomised controlled trial of early introduction of allergenic foods to induce tolerance in infants	Dr Michael Perkin *(King's College, London)*
3.45 – 4.00	Questions	
4.00 – 4.15	Tea and coffee break	

Session Eight **Horizon Scanning**

Chair - Professor Ian Kimber

4.15 – 5.15	Horizon scanning for contractors and other review participants

Close of meeting for contractors and delegates

Thursday 21 February 2008

Day Three: Closed meeting for Review Panel and FSA staff only

Annex 6

Biographies of the 2008 Food Allergy and Intolerance Research Programme Review Panel

Chair of the Review Panel

Professor Peter Aggett

At the time of the T07 Programme Review, Peter Aggett was Head of the Lancashire School of Health and Postgraduate Medicine at the University of Central Lancashire, Preston, UK. He was previously Head of Nutrition Diet and Health, and an Assistant Director at the Institute of Food Research, Norwich. His clinical interest is in Paediatric Nutrition and Gastroenterology, and his research has been on trace element needs in health and disease. He is a past member, and Vice Chair, of COT, and he chaired its Working Group on Food Intolerance that reported in 2000, subsequently participating in project and grant reviews of research arising from this initiative. He is a member and Vice Chair of the Scientific Advisory Committee on Nutrition, and he has also participated in a variety of EC, EU, WHO, IPCS, FAO, UNU activities and task forces on nutrient requirements and safety, and nutrient and environmental risk assessment.

Review Panel Members

Professor Judith Buttriss

Professor Judith Buttriss took over the role of Director General of the British Nutrition Foundation (BNF) on 1st October 2007, having been the BNF's Science Director for almost 10 years. She is a Registered Public Health Nutritionist and has been a member of a number of national committees concerned with funding research, and with public health and nutrition issues. She has contributed extensively to UK government activities in this area, including work on nutrient profiling and on signposting for the Food Standards Agency. She has also contributed to work on obesity in children for the Department of Health, and on the Family Food Survey for Defra. She was also a member of the UK's former Joint Health Claims Initiative Expert Committee since its inception. She has a wide range of research interests in the area of nutrition and its communication, and is currently workpackage leader (dissemination) for 2 EU Framework Programme 6 projects and involved in the work of several other EU-funded activities.

Dr Clare Mills

Dr Mills achieved her PhD in Biochemistry in 1984 (University of Kent at Canterbury, UK). She has had number appointments over her career: 1979-1980, Glaxo Group Research, Ware, UK; 1983-1984, UK Environment and Toxicology Division, Department of Health, Medical, UK. From 1985 to the present Dr Mills has worked at the Institute of Food Research, Norwich. Dr Mills has been a member of several committees including:

- 2001 Member of Royal Society Expert Group on Genetically Modified Organisms for Food Use.
- 2005 - present Self-task Allergenicty Working Group of the EFSA GMO Panel.
- 2006 - present Advisory Committee on Novel Foods and Processes.
- 2007 - BBSRC DRINC Initiative Steering Group.

Dr Mills is a protein biochemist interested in the structure-function relationships in food proteins. Recently her research has been focussed on how processing can affect the allergenicity of foods and why some proteins, and not others, become allergens.

Dr Ingrid Malmheden Yman

Dr. Ingrid Malmheden Yman is a licensed pharmacist with a doctor's degree at the faculty of Medicine, Uppsala University. From 1984 Dr Ingrid Malmheden Yman has been employed by the National Food Administration, Uppsala. The main tasks have been the development and application of immunological methods for the identification of proteins like milk, egg, nuts, legumes, seeds and cereals in food. Since 1996 the laboratory also introduced DNA techniques as a complement to protein analysis. Dr Malmheden Yman participated as national expert in the SCOOP task "On the occurrence of severe food reactions in the EU" 1997-1998. She was a delegate in the expert consultation by FAO/WHO "Evaluation of allergenicity of genetically modified food" in Rome, 2001 and was appointed 2003 as Swedish delegate in the CEN/TC 274 WG 12 "Detection of potential allergens in foodstuffs" elaborating method standards for allergens. Dr Malmheden Yman is a member of the ILSI expert group on allergic reactions registries from 2007. Dr Malmheden Yman has participated as expert supporting the Swedish delegations in Codex Committee on Food Labelling (allergens) and Codex Committee on Nutrition and Foods for Special Dietary Uses (gluten standard).

Professor Paul Garside

Professor Paul Garside is currently the Director of the Centre for Biophotonics at the University of Strathclyde.

His research centres on understanding immunoregulation by tracking cellular and molecular interactions *in vivo* with a view to improving therapy for autoimmune and inflammatory disorders and the design and use of vaccines. A PhD on intestinal helminths sparked his interest in mucosal immune responses and he spent his postdoctoral years studying various aspects of mucosal immunoregulation. He maintained his interest in immunoparasitology being involved in studies delineating the roles of protective and pathological immune responses in gastrointestinal helminth infections. A Wellcome Trust Career Development Fellowship was spent with Professor Marc Jenkins where he was involved in developing systems to examine antigen-specific T and B lymphocyte interactions directly *in vivo*. Investigating immunological events *in vivo* and developing the technology to do so, has resulted in studies examining lymphocyte and APC interactions in a variety of scenarios. It has also provided information on how TH1 and TH2 responses develop, the mechanisms and efficiantcy of DNA vaccination, the impact of infection on immune responsiveness and the regulation of autoimmunity. More recently, he has been involved in studies employing multiphoton microscopy to show the real time interactions of antigen-specific T cells during the development of immune responses *in vivo*.

Professor Anthony Frew

Professor Tony Frew trained in Cambridge, London, Nottingham, Oxford and Stoke-on-Trent. He became interested in allergy while working with Barry Kay at the Royal Brompton Hospital, London and undertook post-doctoral research in Vancouver, Canada. After 13 years in academic positions in Southampton he moved in 2005 to the new medical school in Brighton. His main research interests have been the mechanisms of allergy, health effects of air pollution, and clinical trials of allergen immunotherapy; he has published over 200 papers and reviews in the peer-reviewed literature. Prof Frew has an active clinical practice, in clinical allergy, respiratory medicine and acute general internal medicine. He has served on the Council of the British Society for Allergy & Clinical Immunology (BSACI) since 1993 and is immediate past-president of the European Academy of Allergology & Clinical Immunology (EAACI). He spent 8 years on the editorial board of the Journal of Allergy & Clinical Immunology (3, as associate editor). He sat on the Department of Health Committee on the health effects of air pollution, and in 2004-05 he convened and chaired a European working group on the role of nutrition in allergic disease.

T07 Programme Advisor

Professor Ian Kimber

Professor Kimber has been the Programme Advisor to the T07 Food Allergy and Intolerance Research Programme since the Agency's inception in 2000.

Professor Kimber is currently Professor and Chair of Toxicology at the University of Manchester. Previous to that he was Head of Research and Principal Fellow at the Syngenta Central Toxicology Laboratory. He has broad research interests based around immunotoxicology, allergy and skin biology with specific research themes currently including: the pathogenesis of food allergy, the stimulation of T lymphocyte responses by skin sensitising chemicals and respiratory allergens, and the molecular regulation of Langerhans cell function and the roles played by these cells in the orchestration of cutaneous immune responses. In addition, Professor Kimber has active interests in the development; validation and application of novel predictive test methods in toxicology, and in research that seeks to reduce, refine and replace the use of animals in safety assessment.

Professor Kimber holds, and has held, a wide variety of positions on national and international expert and scientific advisory committees. Currently these include the following: UK Medical Research Council (MRC) Training and Career Development Board, Special Advisor to the MRC on Industrial Liaison, UK Medicine and Health Regulatory Agency (MHRA) Committee for Safety of Devices, Programme Advisor Food Standards Agency Food Allergy and Intolerance Research Programme, and member OECD Expert Committee on Sensitisation.

He has published over 500 research papers, review articles and book chapters and serves currently on the editorial boards of Toxicology, Immunology, Dermatology and Pathology journals.

Professor Kimber has received a number of awards and prizes. These include: the SmithKline Beecham Laboratory Animal Welfare Prize (2000), the 9th Robert A Scala Award in Toxicology, the Doerenkamp-Zbinden Foundation Prize for Realistic Animal Protection in Biomedical Research (2001), Society of Toxicology Enhancement of Animal Welfare Award (2003), and Society of Toxicology Immunotoxicology Career Achievement Award (2005).

Annex 7

T07 Research Project Summaries

Summaries of the 18 T07 research projects that were included in the Programme Review are given below. These are largely as written by the contractor except for minor editorial changes and the sections headed 'rationale for funding', which were written by the Agency and reflect the text published as part of the research requirement under which the research was originally commissioned. The project summaries (study design and aims, results and conclusions) remain unedited (unless otherwise stated, apart from minor formatting changes and the addition of text to add clarity where necessary) abstracts submitted by contractors or executive summaries taken from final technical reports.

Systematic Review on Tolerable Levels of Gluten for People Medically Diagnosed with Coeliac Disease

Mrs Norma McGough
Coeliac UK

Project team
Anthony K Akobeng and Adrian G Thomas

Project number: T07048

Start date: 1st February 2006 **End date:** 31st September 2006

Rationale for Funding the Research

Although avoidance of gluten is necessary in coeliac disease (CD), the exact relationship between the quantity of gluten consumed and the development of symptoms and/or mucosal abnormalities is not clearly understood. In November 2005, new food labelling legislation came into effect that required the declaration of the deliberate addition of 12 allergens wherever these are used as ingredients in prepacked foods. Cereals that contain gluten were included in this list to enable coeliac patients to avoid this ingredient. The results of this study would inform international discussion within Codex on the level of gluten that would be permitted in gluten-free foods. Research Proposals were therefore invited to review the published scientific literature on thresholds levels of gluten affecting the gut mucosa in coeliac individuals.

Study Design and Aims

The aim of this study was to systematically evaluate scientific articles that investigated threshold amounts of gluten which people with CD can tolerate, or threshold concentrations of gluten in food products that can safely be consumed by people with CD. The design of the project was a systematic review of studies published between 1966 and March 2006.

Twelve studies met the review criteria. A daily consumption of 200 mg or more of gluten clearly induced mucosal abnormalities. In 2 studies, the ingestion of an average of 34 - 36 mg of gluten daily did not cause histological changes or clinical symptoms. However, in 1 study, a much smaller dose of gluten (1.5 mg daily) triggered symptoms. The effect of the consumption of gluten-free products with different degrees of gluten contamination was also inconsistent.

Results and Conclusions

The current level of 200ppm of gluten which was set in the 1983 Codex Standard for Gluten-Free Foods, does not seem to be protective for **all** people with coeliac disease and so there may be a case for lowering the current maximum level of gluten permitted in foods. However, there does not appear to be evidence to support a single definitive threshold of gluten that would be tolerated by all patients with CD. The key issue is the total amount of gluten consumed rather than the concentration of gluten in the food products. The higher the threshold or standard, the greater the likelihood of exceeding the safe dosage due to the additive effect.

The project has highlighted the strengths and weaknesses of the existing published research available and enables the Agency to have a better understanding of the scientific basis of the threshold standard for gluten-free labelling purposes. It has also helped to identify the research necessary in this area and implications for future research funding. It is clear that the amount of gluten tolerated by people with coeliac disease varies but the reason for this is unclear. Future studies should investigate potential reasons which may explain the variable response to gluten.

Factors Influencing the Susceptibility to and Characteristics of, Kiwi Allergy.

Dr Jane Lucas
University of Southampton

Project team
Professor John Warner, Professor Jonathan Hourihane, Karen Collins, Kate Grimshaw, Snita Bansal, Lesley Gudgeon

Project number: T07025

Start date: April 2001 **End date:** September 2003

Rationale for Funding the Research

It is unclear what predisposes people to immunologically mediated reactions to food. The Agency identified a need to expand knowledge of the cellular and molecular basis of food allergic disease, to enable predictive markers to be developed. A broad research requirement was therefore issued by the Agency inviting research proposals to identify individuals who might be susceptible to developing food allergy. This project was commissioned from that research call.

Study Design and Aims

The objective of this project was to conduct the first study of kiwi fruit allergy in the UK and the largest clinical study of the allergy worldwide. Specific aims included: to describe the clinical characteristics of kiwi fruit allergy; to evaluate methods of clinical investigation of kiwi fruit allergy; to identify the importance of other allergies in the susceptibility to kiwi fruit allergy; to describe how age influences the onset and severity of kiwi fruit allergy; and, to investigate whether gold kiwi fruit is an allergen.

Subjects with self-reported kiwi fruit allergy were recruited from 3 sources: from the paediatric and adult allergy clinics at Southampton General Hospital, respondents to an advertisement in Anaphylaxis Campaign Magazine and people who contacted the study following a media release on national radio and in newspapers. All subjects were asked to complete a postal questionnaire which consisted mainly of closed questions about their allergy to kiwi fruit, and associated allergies. Subjects who wished to participate further in the research could have blood taken locally which was sent to the research centre for IgE analysis. People who wished to travel to the research centre were invited to attend for a food challenge, skin testing and a blood test. Five subjects who were allergic to traditional green kiwi fruit also had a food challenge to the newly available gold fruit (Zespri ^{TM} Gold).

Results and Conclusions

Questionnaires from 273 subjects with self-reported kiwi fruit allergy were analysed. The age of respondents at the time of their first reaction ranged from 4 months to 71 years. 33 were under 5 years. Respondents reported very little allergy to kiwi fruit in the 1970s, particularly in the now adult population who were children at the time. Reports of allergy were increasingly common in the 1980s, but it was not until the 1990s that kiwi fruit allergy was recognised in children and young infants. Young children with the allergy usually react on their first known exposure and 40% have severe reactions. Adults often react after numerous uneventful exposures and are less likely to report severe symptoms.

Fifty percent of 45 subjects with a history suggestive of kiwi allergy, had their allergy confirmed by a double blind placebo controlled food challenge. This is a relatively high rate of positive food challenges in comparison to many studies of food allergy. Many of the food challenges were inconclusive. We believe this reflects the technical difficulties of conducting food challenges in subjects with oral allergy syndrome. Skin testing using fresh kiwi fruit was a sensitive method of confirming kiwi fruit allergy, but had a high rate of false positive results in this population. Skin testing using commercially available skin test solution had very poor sensitivity when compared with food challenge. Zespri ^{TM} Gold produced allergic reactions in some subjects who are allergic to 'traditional' kiwi fruit.

The main conclusions from the project were as follows:

- Kiwi fruit allergy in the UK is not uncommon.
- Reactions may be severe, particularly in young children and infants.
- A new food should not be immediately categorized as having low allergenicity just because the first reactors (usually adults) have mild symptoms: children may react differently.
- Current methods of clinical investigation of kiwi fruit allergy are not satisfactory. Work is required to improve food challenge protocols (particularly for oral allergy syndrome), commercially available skin test extracts and the CAP system for kiwi fruit. This finding is in keeping with studies of other fruits involved in oral allergy syndrome.
- Gold kiwi fruit is an allergen. People allergic to 'traditional' kiwi fruit are at risk of allergy to Zespri ^{TM} Gold kiwi.
- Post marketing surveillance is required to monitor whether people without allergy to 'traditional green' kiwi fruit develop symptoms to the gold fruit.

The Characteristics of Kiwi Fruit Allergy

Dr Jane Lucas
University of Southampton

Project team
Professor John Warner, Dr Jonathan Hourihane, Dr Stella Lewis

Project number: T07038

Start date: January 2003 **End date:** December 2005

Rationale for Funding the Research

This project built on a previous Agency funded study T07025, which investigated the factors influencing the susceptibility to, and characteristics of kiwi fruit allergy. It was considered that this follow-on project would enable the Agency to determine the characteristics and severity of this emerging allergy in the UK. It is an example of an introduction of a new food allergen into the UK diet, and would inform the Agency's advice to consumers with kiwi allergy. The research team at the University of Southampton provided the Agency with a unique opportunity to utilise a UK cohort of kiwi allergic individuals for further study.

Study Design and Aims

There has been very little research into this allergy and no studies in the UK. Agency funded T07025 confirmed that kiwi fruit allergy appears to be increasingly common and that the reactions can be severe, especially in young children. This study builds on those findings. In particular, the aims were to use kiwi fruit as a model, to provide an illustration of the way in which post-marketing surveillance should be conducted to detect allergy to newly introduced foods; to investigate what proteins in kiwi fruit are responsible for causing allergic reactions. To understand how digestion of kiwi fruit affects it's potential to cause allergic reactions; and to investigate whether people with kiwi fruit allergy are likely to be allergic to Zespri™ Gold.

People with symptoms of kiwi fruit allergy were invited to complete a questionnaire with details about their allergy. Some of these people also had allergy testing: skin tests, blood tests (specific IgE) and food challenges. A small group of people had a food challenge with Zespri™ Gold.

Laboratory investigations studied the kiwi fruit proteins involved in causing allergy. Additionally blood from allergic volunteers was used to study the antibodies that cause people to be allergic. To investigate the effects of digestion on the allergenicity of kiwi fruit, it was digested under laboratory conditions and blood from allergic individuals was used to determine whether they would still react to the digested proteins.

Results and Conclusions

The results of this study confirmed that kiwi fruit should be considered a significant food allergen, capable of causing severe, life-threatening reactions. Young children and infants with kiwi fruit allergy usually reacted the first time that that they ate the fruit and reactions were often severe. Although some adults also have severe reactions, they were more likely to have milder symptoms.

It was demonstrated that the methods currently used to detect food allergy are not always accurate. Attempts were made to improve the accuracy of tests, but further work is required. It is also suggested that there is a need for post-marketing surveillance of new foods as it is not possible to identify allergy to a new food as a significant problem until it a large number of people have developed allergy. Even a large allergy clinic will not register it, as a problem at an early stage.

The project detected 12 proteins that people with kiwi fruit allergy react to. The kiwi fruit protein, actinidin, has commonly been reported to cause allergy in other European countries. However, it was not the cause of allergic reactions in the UK population studied in this project. During digestion studies, most of the kiwi fruit proteins were digested to products no longer capable of causing allergic reactions, but some proteins persisted and would continue to be a potential cause of allergy. Patients with a history of severe reactions to kiwi fruit reacted to proteins that were resistant to digestion. Patients with mild symptoms, confined to the mouth reacted to proteins that are labile to digestion and are easily destroyed in the stomach. Infants have a relatively high gastric pH and under these conditions kiwi fruit protein digestion is incomplete. Infants are therefore potentially more likely to react to proteins in kiwi fruit.

This was the first study to report the immunogenicity and clinical allergenicity of gold kiwi fruit, demonstrating that people with kiwi fruit allergy are at risk of developing allergy to gold kiwi fruit.

Qualitative Research into the Information Needs of Teenagers with Food Allergy and Intolerance

Celia Watts
COI Communications

Project number: T07045

Start date: January 2005 **End date:** May 2005

Rationale for Funding the Research

The Agency identified a policy need to understand the information needs of teenagers with regard to food allergy and intolerance, as a particularly vulnerable sub-group of the allergic population. Qualitative research was therefore commissioned to explore the information needs of consumers, in relation to food allergy and intolerance. It was a particular requirement to explore the behaviour and information needs among teenagers and young adults with these conditions and how to better connect them to, and provide them with, the information they need.

Study Design and Aims

The aim of the project was to carry out qualitative research to establish the information needs of teenagers and young people with food allergies and intolerance. It also aimed to explore how best these needs can be met and how better to communicate with children and young people.

Stage I of the research involved group discussions and in-depth interviews involving teenagers and young people with food sensitivities, and parents and children with food sensitivities. Stage II of the research comprised an interactive workshop, involving young people with food sensitivities, parents, representatives from the Food Standards Agency, COI, and professionals involved in the field of food sensitivity.

Results and Conclusions

The findings of the project suggested that the way individuals deal with their food sensitivity can be very variable, with many factors combining to impinge on attitudes, behaviours and needs – for example severity, age of onset/diagnosis, personality/mindset and parenting style. Food sensitivity is felt by young people to have many 'downsides', including: feeling 'different'; effect on social and inter-personal life; vulnerability to lack of sympathy/teasing/bullying; unpleasant symptoms; dietary restrictions. These difficult feelings, coupled with 'normal' teenage angst, can lead to resentment and denial, with increased risk of adverse reactions – counterbalanced to a greater or lesser extent by growing maturity and a desire for independence.

Parents agreed that food sensitivity adds an extra element to the ordinary challenges of life with a teenager. Parents could feel very overwhelmed at diagnosis, and while they learned to manage the situation, they were also prone to difficult feelings such as anxiety, guilt and isolation. They too identified the problems of restrictions on diet and less spontaneity in family life, as well as financial issues and fears for the future.

There were widespread criticisms of inconsistencies in food labelling relevant to food sensitivities, and a desire for clear, well-presented information using colour coding and symbols.

As the child enters and moves through the education system, there are anxieties at each time of change. While most were more or less satisfied with how food sensitivity was managed at the nursery, infant and primary stages, there were significant concerns about secondary school. The greater freedom of secondary school, coupled with peer pressure and the need to make friends, may put particular strain on food sensitive young people's self-management. These strains are redoubled at the time of transition to university or college, especially if this also involves a move out of the parental home. Living independently presents many challenges, related to shopping, cooking, eating in 'catered' environments and self-catering in shared accommodation. Often the process of adjustment was described as 'trial and error', with evident risk of adverse reactions.

More frequent adverse reactions among teenagers and young people are/were believed to be due to a number of factors: insufficient 'training' leading to faulty risk assessment; the stress of change and new situations; 'normal' teenage feelings exacerbated by difficult feelings around the food sensitivity; peer pressure; more 'risk opportunities'; time lag between removal of the parental safety net and development of self-care; late onset/ diagnosis.

Eating away from home can be an especially problematic. Eating out as a family is the least risky, though there are issues around restricted choice of venue and meal, doubts about the ability/willingness of staff to respond constructively, inadequate menu information, and fear of embarrassment. Because eating out is such an important part of our culture, food sensitive young people and their parents have to work out coping strategies.

As regards information sources, usage and needs, we found wide variations in respondents' propensity to seek out information. Where respondents had sought and/or received information, this came from a wide range of sources. Only a minority of respondents had actively sought information, the majority being passive recipients.

There was also a widespread feeling that information and 'consciousness raising' about food sensitivity was needed in the wider world: health, education, catering, retailing and the general public. There had been only limited use of the internet as an information channel, but it was agreed that it had a potentially strong role to play.

Discussions at the interactive workshop supported the concept of risk 'hot spots' as young people take increasing responsibility for their food shopping and food preparation, with the method of diagnosis, and the transition from primary to secondary school, again identified as especially worrying times.

As regards food labelling, workshop participants in some instances had rather ambitious ideas around symbols and colour coding. However, there was some consensus that a universally recognised 'Allergy' symbol on the front of pack, and a consistent approach to the provision of clear allergen information on the back/side of pack, would go a long way towards empowering people with food sensitivities to make their own decisions about the suitability of the product for them.

The third topic discussed at the workshop, eating out, was confirmed as a key area and one where appropriate information and help were not always available. Participants wanted clear written information about ingredients and allergy risks, and access to knowledgeable and responsive staff within the catering establishment. Chef cards were felt to have some potential.

Chronic and Acute Effects of Artificial Colourings and Preservatives on Children's Behaviour

Professor Jim Stevenson
University of Southampton

Research team
Professor Edmund Sonuga-Barke, Professor John Warner and Dr Donna McCann

Project number: T07040

Start date: September 2004

End date: **Main project:** 28 February 2007
Analysis of acute challenge metabolite samples: 28 February 2008

Rationale for Funding the Research

Possible links between behavioural changes in children and certain food additives continues to be a source of concern for some parents. In 1997 MAFF commissioned a 3 year study to investigate the possibility of a link between consumption of certain artificial food additives and behaviour in children. Independent experts reviewed the results of that research and concluded that whilst the study findings were consistent with published reports of behavioural changes occurring in some children following consumption of certain food additives, it was not possible to reach firm conclusions about the clinical significance of the observed effects. Recommendations were made for further research that would assist the Agency in developing evidence-based policies and providing advice for consumers. Proposals were therefore invited to examine, (using guidance on study design issued by the Committee on Toxicity) whether there are any links between certain food additives and behaviour in children.

Study Design and Aims

There has been a longstanding suggestion that certain artificial food colours and certain preservatives (AFCA) influence behaviour in children. It is over 30 years since Feingold made his initial claims of the detrimental effect of AFCA on children's behaviour. The main proposed putative effect of AFCA is to produce overactive, impulsive and inattentive behaviour, i.e. hyperactivity, which is a pattern of behaviour that shows substantial individual differences in the general population. Children who show this behaviour pattern to a marked degree are likely to be diagnosed with Attention Deficit Hyperactivity Disorder (ADHD). Despite the failure of early studies to identify the range of proposed adverse affects, a more recent meta-analysis of double blind, placebo controlled trials have shown a significant effect of AFCA on the behaviour of children with ADHD. The possible benefit in reducing the level of hyperactivity of the general population by the removal of AFCA from the diet is less well established.

There is some evidence from the earlier study on the Isle of Wight (funded by the Agency under project code T07004) of adverse effects on hyperactivity measured by parental ratings for 3 year old children on 1 mix of artificial food colours and preservative. These findings required replication on 3 year old children and to establish if the effects were also evident using a wider range of measures of hyperactivity. The present community based double blinded, placebo controlled food challenge (DBPCFC) was designed to extend the age range studied to include 8/9 year old children to determine if the effects could also be detected in middle childhood.

Results and Conclusions

The results show that certain mixtures of artificial colours and sodium benzoate preservative (referred to as Mix A and Mix B) increase the average level of hyperactive behaviour of children in some age groups compared with a placebo.

The results replicate and extend the findings from the earlier Isle of Wight study. The specific findings were that with Mix A there was a significant ($p < 0.05$) adverse effect on the average hyperactive behaviour of 3 year old children as measured using the chosen outcome measure of a Global Hyperactivity Aggregate (GHA) and based on the primary analysis of the study (the whole cohort). In contrast, Mix B was without significant effect on the behaviour of 3 year old children. The reverse picture was seen with 8/9 year old children. In this case, compared with placebo, Mix B had a significant adverse effect on the behaviour of children ($p < 0.05$). However, for the whole cohort Mix A was without significant effect on the behaviour of 8/9 year old children.

The importance of these findings is that they confirm that the adverse effect of certain artificial food colours that have been implicated in children with hyperactive syndromes can also be demonstrated in 2 samples taken from the general population. Although the results of the study suggest that some mixtures of certain food colours and benzoate preservative may affect the level of hyperactive behaviour in children, removal of these additives would not be a panacea for ADHD.

Prevalence and Incidence of Food Allergies and Food Intolerance – a Prospective Birth Cohort Study to Establish the Incidence and a Concurrent Cross-Sectional Study of Whole Population Cohorts at 1, 2, 3, 6, 11 and 15 Years

Professor Tara Dean
The David Hide Asthma and Allergy Research Centre, St. Mary's Hospital, Newport, Isle of Wight

Project team
Dr Carina Venter, Dr Brett Pereira, Dr Kerstin Voigt, Jane Grundy, Bernie Clayton and Gill Glasbey

Project number: T07023

Start date: July 2001 **End date:** August 2006

Rationale for Funding the Research

The number of individuals suffering from allergic reactions to food appeared to be increasing. The basis for this increase and the inter-individual susceptibility to food allergy required further study. There was also a need for better prevalence and incidence data in the UK for both food allergy and intolerance. Proposals were therefore invited to investigate the prevalence of food allergy and to assess whether and to what extent this was increasing.

Study Design and Aims

It was the aim of this study to 1) investigate the prevalence and incidence of Food Hypersensitivity (FHS) in children, looking primarily at the cumulative incidence of FHS over the first 3 years of life and the prevalence of FHS in older children and teenagers (6, 11 and 15 years) and 2) establish temporal changes in sensitisation to foods over the last 2 decades. Different birth cohorts were recruited to participate in this latter part of the study. The study was carried out on the Isle of Wight.

All children were approached for skin prick tests (SPT) to a standard battery of food and aero-allergens. Children were identified for food challenges taking into account their reported history and SPT result.

Results and Conclusions

Over the course of the 3 years in which the birth cohort were followed 942 (97.2%) children were seen at either 1, 2 or 3 years, with 807 children seen at 1, 2 and 3 years. At 1,

2 and 3 years, the rate of sensitisation to any food allergen was 2.2%, 3.8% and 4.5%. Over the course of the 3 years 5.3% children had a positive SPT to any food in the pre-defined Panel.

Adverse reactions to food were reported by 7.2% of parents at 12 months of age, 8.9% at 2 years and 9.2% at 3 years. Of the 807 children seen at 1, 2 and 3 years, 272 (33.7%) reported a food related problem. Based on Open Food Challenge (OFC) and a good clinical history, the prevalence of FHS was 4% at 1 year, 2.5% at 2 years and 3.0% at 3 years. Based on Double Blind Placebo Controlled Food Challenge (DBPCFC) and a good clinical history, the prevalence of FHS was 3.2% at 1 year, 2.1% at 2 years and 2.9% at 3 years. Cumulativly by 3 years of age, 6.0% of children were diagnosed with FHS based on OFC and history and 5.0% of children based on DBPCFC and history. Overall the foods implicated in this study were milk, egg, peanut, corn, potato, tomato, salicylates and wheat.

Only 16.1% of children who were seen at 1, 2 and 3 years of age and reported a food related problem were diagnosed with FHS by means of an OFC and history and 12.9% by means of a DBPCFC and history.

Comparing the information of the 3 year olds with children (aged 4 years) born 12 years earlier on the Isle of Wight, the results indicated that there was no increase in sensitisation to food allergens (p= 0.3). Very importantly, this study was able to compare the FHS incidence rates with those previously obtained in a US study by Bock. In this USA study, of the 501 children enrolled into the study, 37 (7.4%) were diagnosed with FHS by means of either OFC or DBPCFC. In our study, of the 969 children enrolled into the study, 6.0% (58/969, CI: 4.6 – 7.7) children were diagnosed with FHS based on OFC and history and 5.0% (48/969, CI: 3.7 – 6.5) children based on DBPCFC and history. Using either the OFC or DBPCFC outcome, the difference in incidence was not statistically significant.

For the school cohorts, 798, 6 year olds, 775, 11 year olds and 757, 15 year olds were recruited into the study. 3.6% (6 year olds), 5.1% (11 year olds) and 4.9 % (15 year olds) had a positive SPT to any of the food allergens. A total of 94 (11.8%) 6 year olds reported a problem with a food or food ingredient, 11.6%, 11 and 12.4%, 15 year olds. Based on open food challenge and/or suggestive history and positive skin tests, the prevalence of food hypersensitivity was 2.6% in the 6 year old cohort. Based on a clinical diagnosis or suggestive history and positive skin tests, the prevalence was 1.6%. The corresponding figures were 2.3% and 1.4% for the 11 year olds and 2.3% and 2.1% for the 15 year olds. Amongst the school cohorts the foods most commonly implicated in FHS were milk and milk products, peanut, wheat, banana, sesame, tree nuts, egg, shellfish, gluten (coeliac disease), green beans, kiwi, tomato and additives. FHS was confirmed by OFC and a good clinical history in only 21% (20/94) 6 year olds, 20% (18/90) 11 year olds and 18% (17/94) of the 15 year olds who reported a food problem.

The key findings from this study therefore indicate that, reported adverse reactions to foods are common in all age groups, but rates of diagnosed FHS are low. Looking at the rates of FHS in each age group, the FHS rate ranged between 1.4% based on DBPCFC and a good clinical history at age 11 years and 3.0% based on DBPCFC and a good clinical history at 1 year. Additionally, considering the birth cohort, we have found that sensitisation to foods have not increased over the last 2 decades. In the light of the discrepancy between reported and diagnosed FHS, the major implication of this study is the need for accurate diagnosis to prevent children being on unnecessary restricted diets.

An Investigation into Trends of Peanut Allergy Incidence in the Last 15 Years in England Using Sequential Childhood Cohorts

Professor Tara Dean
The David Hide Asthma and Allergy Research Centre, St. Mary's Hospital, Newport, Isle of Wight

Project team
Dr Carina Venter, Jane Grundy and Jo Turke

Project number: T07034

Start date: April 2003 **End date:** March 2006

Rationale for Funding the Research

The Department of Health's COT report (published in 1998) on peanut allergy, advised that pregnant and breastfeeding women may wish to consider avoiding consumption of peanuts if their child has a family history of allergic disease, and that peanut and peanut products should not be introduced into the diet until 3 years of age. There was a need to establish the impact of this advice and if the incidence of peanut allergy has changed since the advice was issued. Proposals were therefore invited to determine whether and to what extent the incidence of peanut allergy has changed since the COT's advice to pregnant and breastfeeding mothers from atopic backgrounds.

Study Design and Aims

There was a need to establish whether the advice issued by the COT had led to a change in the incidence of peanut allergy. In addition, to establish what impact, if any, this advice has had on the maternal consumption of peanut during pregnancy and breastfeeding. This project utilised 3 cohorts of children born on the Isle of Wight over a 12 year period to address these questions.

Results and Conclusions

969 women were recruited during pregnancy and food intake was established with a validated food frequency questionnaire from 937 women. All mothers were living on the Isle of Wight and had a delivery date between August 2001 and September 2002. Food avoidance during breastfeeding was also assessed from 614 women who breastfed ≥ 1 week. 445 (47.5%) women reported complete avoidance of peanuts, another 57 (6.1%) did not exclude peanut but never actually ate any and 360 (38.4%) did eat peanut. Although it is quite likely that women who reported complete avoidance were actually exposed to traces/hidden nuts. The majority of the pregnant women consumed milk (88.7%) and wheat (91.5%) frequently and white fish moderately (83.5%). With regards to egg intake, the

question on egg intake showed a low validity and reliability and was therefore not included. 42% of mothers who responded recalled knowledge of the COT report but this awareness was not linked to family history of atopy. 52% of mothers who had heard of the advice reported changing their peanut consumption when pregnant with over 90% reporting to have either stopped eating peanuts completely or stopped eating foods containing obvious peanuts.

Data collected during the breastfeeding period indicated that in total, 265/614 (43.1%) mothers avoided 1 or more foods from their diets. These included a wide variety of foods such as the major food allergens, citrus, meat, spicy foods, onion, brassica family, shellfish and strawberries. Of the 265 mothers, 173 avoided some of the main allergenic foods, with 39 avoiding more than 1 of the main food allergens.

The study investigated the influence of maternal diet during pregnancy and breastfeeding on food hypersensitivity (FHS) and sensitisation in the infant during the first 2 years of life. It was found that maternal dietary intake during pregnancy, and breastfeeding duration did not appear to influence the development of sensitisation to food allergens or FHS.

As nearly half of the mothers reported avoiding peanuts, the study also investigated the impact this may have had on their lives and their families lives. Mothers who had avoided peanuts as well as mothers who did not avoid peanuts during pregnancy and breastfeeding were interviewed. Emergent themes included: variations in information provision and the range of avoidance tactics adopted by participants; a lack of clarity in relation to information and advice about peanut avoidance, the risks entailed and the introduction of peanuts to the developing child's diet; the importance of experience of atopy in influencing participants' decisions to avoid peanuts and the importance of individuals' choices in the decision making process. It was therefore concluded that improvements to the experience of avoidance and/or non-avoidance of peanuts were primarily focused around the provision of information and advice. In particular, a need for clear, consistent factual information and advice about the real risks associated with peanut consumption during pregnancy/lactation, and to whom these risks apply.

The project also addressed the question of whether there has been a change on sensitisation rate and symptomatic allergy to peanuts during the last decade or so. This was done by comparing the birth cohort born between 2001-2002 (cohort C) (post COT report) and reviewed at 3 years of age to 2 cohorts born prior to the publication of the COT report (a cohort of children born in 1989 (cohort A) and reviewed at 4 years of age, and a cohort born between 1994-1996 (cohort B) and reviewed at 3 years of age). Fisher's Exact test indicates a significant difference in both sensitisation and reported allergy across the 3 cohorts. However, there was no statistical significant change in sensitisation to peanut between cohort A and C and cohort B and C. Comparing the 3 different cohorts there were no significant changes between reported peanut allergy in cohort A and C, but it did

significantly drop between cohort B and C. In terms of clinical allergy, there was a change over time, explained by the significant increase in peanut allergy between children born in cohort A and cohort B. The overall prevalence of atopy in the 3 cohorts followed a similar pattern with raised levels being reported in cohort B. Although Fisher's Exact test indicated no overall difference between cohorts ($p = 0.083$) and no pairwise comparison between cohorts reached significance at the conventional 5% level the quadratic component of trend was found to be statistically significant ($p = 0.0224$).

In conclusion there have not been significant changes (either increase or decrease) in peanut allergy or sensitisation since the release of the COT report. It was further considered unlikely that the COT report could have a significant effect on these figures, as the "wrong" group of mothers (i.e. first time mothers opposed to mothers from atopic families) avoided peanuts. Also, the increased rate in overall atopy of cohort B compared to cohort C, may just indicate that the lower levels of sensitisation to peanuts seen in cohort C is merely a reflection of the global trend rather than the effect of the COT report. Additionally, we did not collect any information on peanut consumption during pregnancy and breastfeeding from the mothers of cohorts born prior to the publication of the COT report and a direct comparison cannot be made.

The Prevalence of Peanut Allergy in British Children at School Entry Age in 2003-2004

Professor Jonathan Hourihane
University of Southampton and then University of Cork, Ireland

Project team
Dr Stephen R Roberts, Wythenshaw Hospital, Manchester

Project number: T07035

Start date: April 2003 **End date:** March 2005

Rationale for Funding the Research

The Department of Health's COT report (published in 1998) on peanut allergy, advised that pregnant and breastfeeding women may wish to consider avoiding consumption of peanuts if their child has a family history of allergic disease, and that peanut and peanut products should not be introduced into the diet until 3 years of age. There was a need to establish the impact of this advice and if the incidence of peanut allergy has changed since the advice was issued. Proposals were therefore invited to determine whether and to what extent the incidence of peanut allergy has changed since the COT's advice to pregnant and breastfeeding mothers from atopic backgrounds.

Study Design and Aims

Mothers of children entering school for the first time in 2003-2005 were recruited and completed a detailed questionnaire. Each recruited child had skin prick testing. Children with positive skin prick tests to peanut had peanut challenges (DBPCFC). Causal pathway analysis was undertaken to explore reasons for maternal non-compliance with COT advice.

In this project, we report the prevalence of peanut sensitisation in the first school cohort (2003-2005) to have been conceived after the 1998 COT advice was issued.

Results and Conclusions

1072 mother-child pairs were recruited and studied in school.

61% of 957 mothers recalled hearing the advice about peanut in 1998. This figure was unaffected by maternal atopic status. Only 36 mothers (3.8%) followed the Government's advice by stopping consuming peanut while pregnant. Maternal atopy had no effect on peanut consumption while breastfeeding. Mothers were less likely to change their diet if having 2nd or subsequent child compared to mothers having their first child (OR 0.635, 95% CIs 0.543-0.743, p <0.01). 30 children (2.8%, 95% CIs 1.8-3.8%) had a positive peanut SPT. 20

children (1.8%, 95% CIs 1.1-2.7%) were shown to have peanut allergy. This is the highest prevalence of peanut allergy recorded to date. Causal pathway analysis showed clearly that mothers had been confused about whether COT advice applied to them. We found no significant differences between low risk and high risk mothers in whether or not they recalled the advice. Although mothers were more likely to remember COT advice if it had been given by a midwife, they were only more likely to actually comply with this advice if peanut consumption was already low.

The prevalence of peanut sensitisation in this cohort is 2.8% and peanut allergy now affects 1.8% of British children at school entry. It is difficult to ascertain any impact (either positive or negative) of the UK Government advice on the prevalence of peanut allergy in British children aged 4-5 years old in 2003-2005. Pre-conceptual maternal peanut consumption patterns were an important barrier to change, that must be addressed if planned specific advice is to cause changes of maternal dietary behaviour.

The Prevalence of Food Allergy and Weaning Practices in a Birth Cohort of UK Infants

Dr Graham Roberts
University of Southampton

Project team
Mrs Kate Grimshaw and Miss Erin Oliver

Project number: T07046

Start date: August 2005 **End date:** October 2009

Rationale for Funding the Research

This study was funded as part of a much larger EU framework 6 project (EuroPrevall). EuroPrevall is a multidisciplinary, trans-sectional project involving 17 European member-states as well as 8 additional partners from outside the EU. 1 aim of EuroPrevall is to establish the patterns and prevalence of food allergies across Europe in infants, children and adults. Participation of the UK birth cohort was considered essential to ensure a good geographic spread across Europe and, ensuring different climatic and cultural regions of Europe are appropriately represented. The Agency was approached by the study co-ordinator to fund the UK birth cohort workpackage of EuroPrevall. As this study was part of the larger EuroPrevall project, the original proposal was not submitted in response to a specific Research requirement, although the project aims fit within the remit and research aims of the T07 Programme.

Study Design and Aims

This project (known as the PIFA study) is a birth cohort study that makes up part of EuroPrevall, a multidisciplinary project involving 53 partners with an EU contribution of 14.5 Million Euros (9.6 Million Sterling) that will run for 4 years. The overall objective of EuroPrevall is to deliver the information and tools necessary for policy makers, regulators and the food industry to effectively manage food allergies across Europe and hence deliver an improved quality of life to food allergic consumers. An essential part of EuroPrevall is to characterise the patterns and prevalence of food allergies across Europe in infants (birth cohort studies), children and adults (cross-sectional surveys). To achieve this, birth cohort studies are being run in 8 European countries (Greece, Iceland, Spain, Poland, Germany, Holland, Lithuania and the UK), with the aim of establishing the prevalence of food allergy in babies and infants up to 2 years of age from the general population. The UK birth cohort study is being funded by the Food Standards Agency (as project T07046) and is being carried out in the Winchester and Eastleigh NHS Trust. The project will deliver robust data on the prevalence and types of food allergy and sensitisation found in infants in the UK currently.

Pregnant women have been recruited from 28 weeks gestation. At delivery, cord and maternal blood are taken from all mothers. All parents are then contacted when their infant is 12 and 24 months and complete a telephone questionnaire detailing the child's health, changes in feeding and environmental factors. Infants are not seen for a clinical assessment unless there is a possibility that they have had an adverse reaction to food. If this is the case they are asked to attend the Wellcome Trust Clinical Research Facility (WTCRF) at Southampton General Hospital where they will undergo clinical assessment. 2 age matched infants for each case are also being invited to attend the WTCRF for clinical assessment.

A second research question that the project is seeking to address is to look at the relationship between weaning and feeding practices in the first year of life and the development of atopic disease. Parents are asked to complete weekly food diary sheets on their child's dietary intake during the first year of life in order to collect detailed prospective dietary information on feeding and weaning practices.

Results and Conclusions (to date)

Recruitment was completed at the end of September 2007 with 1204 mother/infant pairs recruited. Refusal rate to take part is 26%. To date 4 women have withdrawn from the study and 11 are lost to follow-up. 3 infants have had to be excluded due them not meeting the recruitment criteria and 1 infant has died. Approx 60% of women have completed and returned food diaries to 6 months.

By the end of September 2007, 101 women had been in touch with the study office concerned that their infant is reacting to a food. Of these 65 were thought to have possible reactions to food so have been assessed at the Wellcome Trust Clinical Research Facility at Southampton General Hospital and of these 37 are thought to have a food allergy. 23 infants have been challenged and 13 are awaiting challenge. Of those challenged, 18 have been diagnosed as being food allergic by double blind placebo controlled food challenge (DBPCFC).

Now recruitment has been completed the emphasis of the study has shifted onto completion of the 12 month questionnaires, diet diary analysis and continuing with the control and symptomatic clinical assessments.

The Role of Peanut-Specific T Cell Responses in Children with Peanut Allergy and in Children who are Tolerant to Peanuts

Professor Gideon Lack
King's College, London

Project team
Dr Victor Turcanu and Dr Susan Chan

Project number: T07041

Start date: April 2004 **End date:** March 2008

Rationale for Funding the Research

Results from previous Agency funded studies suggest that T-lymphocyte responses to peanut antigens were different in those who are allergic and non-allergic to peanut, as well as in those who have outgrown their allergy. There was therefore a need to understand in greater detail the roles played by T-lymphocytes in the pathogenesis of food allergy, and to establish their relevance for diagnosis and prognosis, and as predictors of severity and likely cross reactivity. Particularly to determine the differences that exists between those who are sensitised to food allergens and those who are not. Proposals were therefore invited to determine the role of T-lymphocytes on the pathogenesis of food allergy.

Study Design and Aims

Peanut allergy is an important public health concern because it affects increasing numbers of children in the UK and the ingestion of even minute amounts of peanuts, often found as contaminants in processed foods, may trigger severe anaphylactic reactions.

A better understanding of the immune mechanisms that underlie the establishment of peanut tolerance or, conversely, the development of peanut allergy is essential in order to provide dietary advice leading to the prevention of peanut allergy. Furthermore the characterisation of the immune processes involved in the maintenance of peanut allergy (which is rarely outgrown, unlike most other food allergies) should lead to the design of better therapeutic interventions.

Results and Conclusions (to date)

In the frame of the present project, we have found and reported at previous Agency workshops that IgG/IgE levels and T cell responses to peanut antigens are correlated whereas for non-allergic responses IgG/IgE levels and T cell responses are uncoupled. These studies provide a theoretical basis for the targeting of T cell function in potential immunomodulatory treatments for peanut allergy. As part of this project we have also finalised the investigation of the immunological differences between the proliferative

responses of peanut allergic and tolerant donors. We found that facilitated antigen presentation (FAP) amplifies peanut-specific responses in peanut allergic (PA) but not in tolerant individuals. We also found that PA individuals have a higher frequency of peanut-specific circulating T cell precursors. Conversely, we found that the differences between PA and tolerant individuals with respect to their peanut–specific responses are not caused by different memory-naïve T cell subsets. In fact, in both PA and tolerant individuals' peanut-specific responses are generated by memory T cells.

The last part of this project, on which we are currently working, is aimed at obtaining evidence for the existence of different routes of sensitization to peanut in children. Indeed, despite the requirement for prior contact with an allergen for sensitization to occur, the majority of peanut allergic children react to their first known peanut ingestion. Evidence suggests that sensitization may occur by contact with allergen through the skin. Individuals thus sensitized may be predisposed to developing peanut allergy, whilst tolerance to peanut may be induced by oral exposure. We have employed the use of skin and gastrointestinal homing memory T cell markers (Cutaneous Lymphocyte Antigen (CLA) and $\alpha 4\beta 7$ respectively) to indicate the likely route of initial sensitization and examine the evidence for this theory.

Immunomagnetic beads were used to isolate CLA+ and $\beta 7$+ memory T cells from peripheral blood mononuclear cells. The cells were stimulated with peanut extract in the presence of antigen presenting cells. Thymidine incorporation was assayed to measure lymphocyte proliferation. Stimulation indices to peanut in the CLA+ cells were compared to those in the $\beta 7$+ cells in both peanut allergic and peanut tolerant children. Peanut specific cytokine production including IL4, IL5, IFN-γ, TNF-α, IL10 and IL-13 were batched and measured in cell culture supernatants of both groups.

Higher proliferation was observed in the CLA+ memory T cells relative to the $\alpha 4\beta 7$+ memory T cells in peanut allergy. This trend appears to be reversed in non-allergic patients. In conclusion, *in vitro* evidence supports the hypothesis that sensitization to peanut via the skin may be associated with the development of peanut allergy, whilst oral sensitization may induce tolerance.

The Role of IgG in Allergy and Tolerance to Common Food Allergens

Professor Pamela Ewan
Addenbrookes NHS Trust, University of Cambridge

Project team
Dr Szun Szun Tay, Sr Yvonne King, Mr John Deighton and Dr Andrew Clark

Project number: T07032

Start date: September 2003 **End date:** August 2006

Rationale for Funding the Research

It is considered that the development of food allergy is usually associated with production of allergen specific IgE antibody. However there is strong evidence that both allergic and non-allergic individuals are also able to mount IgG antibody responses to food proteins to which they are exposed. It had been suggested that IgG may even have a protective role. There was therefore a need to explore the ways in which IgG antibody responses may modify or influence the activity of specific IgE antibody and alter the pathogenesis or course of food allergy. Proposals were therefore invited to establish the role of IgG in the development of allergic sensitisation and reactions to food.

Study Design and Aims

The aim of this study was to investigate the role of specific IgG responses in peanut and egg allergy. Serum IgG, IgG1 and IgG4 (in μg/ml) to peanut extract and ovalbumin were compared in children who were egg or peanut allergic and non atopic controls; and also in children with current or resolved egg allergy.

High levels of ovalbumin-specific IgG (IgG1 and IgG4) were found in controls, active and resolved egg allergy, with no significant differences between groups. In the same controls, egg-specific IgG levels were 10-fold higher than peanut-specific IgG. In peanut allergic children, peanut-specific IgG (IgG1 and IgG4) were significantly increased compared to controls and egg-allergic children who were not sensitised to peanuts. Furthermore, peanut-specific IgG and IgE levels were strongly correlated in peanut allergy. However, because of significant overlap between the IgG titres of the peanut allergic and control groups, IgG measurements do not appear to be of diagnostic value.

Results and Conclusions

It was concluded that ovalbumin-specific IgG levels of egg-allergic, egg-resolved or control groups are not distinguishable. Higher peanut-specific IgG levels are associated with clinical allergy, but the range of IgG titres of the allergic and control groups

overlapped, hence ovalbumin and peanut specific IgG measurements do not appear to be of diagnostic value. Strong IgG responses to ovalbumin may be a normal physiological response to a protein frequently ingested from infancy, whereas up-regulated IgG responses in peanut allergy may be indicative of a dysregulated immune response to peanut allergens.

Longitudinal Study of T Cell Responses in Development and Resolution of Food Allergy

Professor Pamela Ewan
Addenbrookes NHS Trust, University of Cambridge

Project Team
Dr Szun Szun Tay, Sr Yvonne King, Mr John Deighton and Dr Andrew Clark

Project number: T07042

Start date: July 2004 **End date:** January 2010

Rationale for Funding the Research

Results from previous Agency funded studies suggest that T-lymphocyte responses to peanut antigens were different in those who are allergic and non-allergic to peanut, as well as in those who have outgrown their allergy. There was therefore a need to understand in greater detail the roles played by T-lymphocytes in the pathogenesis of food allergy, and to establish their relevance for diagnosis and prognosis, and as predictors of severity and likely cross reactivity. Particularly to determine the differences that exist between those who are sensitised to food allergens and those who are not. Proposals were therefore invited to determine the role of T-lymphocytes on the pathogenesis of food allergy.

Study Design and Aims

The aim of this longitudinal study is to follow T cell responses in children during active egg allergy and resolution in order to determine the role of T lymphocyte cells in the persistence and resolution of allergy.

Children with confirmed egg allergy are being followed longitudinally alongside non-atopic children and children who are egg-sensitised but not allergic. Children are challenged annually with baked egg or pasteurised raw egg to confirm their allergic status. Peripheral blood is obtained and ovalbumin-specific T cells that express IFNγ or IL 4 detected by flow cytometry, in order to demonstrate and characterise changes in T cell proliferation and cytokine production in children whose allergy resolves or persists. These data may better inform immunological status than existing immunological markers (such as IgE).

We have recruited our target number of egg allergic children (n=60) and are following them longitudinally. We have developed a novel lymphocyte stimulation assay for studying T cell responses to stimulation with the major egg allergens ovalbumin (OVA) and ovomucoid (OM). This involves measurement of T cell proliferation by CFSE dilution and detection of cellular secretion of cytokines IL 4, IL 10, and IFNγ. We have also begun to measure IL 4, IL 10, and IFNγ in cell culture supernatants at different time points.

Results and Conclusions (to date)

Initial cross-sectional analysis of data from children's first challenges revealed no significant differences in the frequency of OVA-specific T cells, IFNγ or IL 4 expressing cells between controls, egg-allergic or egg-tolerant children.

Thus, all children whether egg allergic or not, had detectable ovalbumin-specific T cells, and no difference in OVA-specific IFNγ or IL 4 production were found in egg allergy, tolerance or controls.

Results of T cell proliferation studies have shown that higher proportions of egg allergic (10/35) and resolved (7/20) subjects had CDI OVA>5.0 compared to controls (1/15). Significantly more children with egg allergy had increased proliferative responses to egg compared with non allergic controls. Cytokine assays have demonstrated that all subject groups responded to OVA stimulation by expressing significant amounts of cytokines, but there were no significant differences between allergic children and non allergic controls.

These results contrast with work by other groups on peanut and milk suggesting Th-2 skewing in allergy. This might be explained by method differences between groups, e.g. using different antibody clones or measuring cytokines in supernatant rather than intracellularly as we have. However, our work agrees with other groups where Th-2 skewing is found in subjects without allergy.

Recruitment is complete and future work includes continuing annual follow-up of children with egg allergy and performing further challenges with cooked or raw egg and T cell assays, these are ongoing. We will also make a comparison between cytokines detected on allergen-specific cells by flow cytometry and cytokine concentrations detected in supernatants of allergen stimulated PBMCs.

Early Life Origins of Food Allergy: Projects T07033 and T07044 (which are linked to a previous Agency funded project: T07005)

Project Titles

The immunomodulatory role of maternal IgG in infant atopic programming (T07033)

Perinatal egg and milk allergen exposure in relation to tolerance or allergic sensitisation to food in infancy (T07044)

Professor John Warner

University of Southampton

Project teams

T07033 – Dr Gillian Vance, Dr Stella Lewis, Dr Kathy Bodey, Norma Diaper and Dr Shute

T07044 – Dr Jane Lucas, Dr Kathy Bodey, Claire Powell, Dr Saul Faust, Laurie Lau and Rita Briggs

Project number: T07033 and T07044

Start date: May 2003 (T07033)
April 2004 (T07044)

End date: 31 August 2005 (T07033)
31 December 2006 (T07044)

Abstract

There has been a progressively increasing prevalence of food hypersensitivity which has paralleled the increases in all allergic diseases over the last 30 years. However, while asthma prevalence rates are stabilising those for anaphylaxis and food allergy are still increasing. Indeed for food allergy the increase in hospital admissions in the UK over the last 15 years is 5 fold and for anaphylaxis 7 fold. Overall prevalence rates for food hypersensitivity in the population are around 3%. However, this is higher in infancy where rates have been quoted as up to 8-10%. The commonest first manifestation of food hypersensitivity is eczema but this is often the first manifestation of an allergic march to asthma and allergic rhinitis. Susceptibility for allergic sensitisation to food allergens is present in very early life and there are credible reasons for believing that the seeds of this problem are sown before birth. However, the relationship between dose and route of exposure of allergens via the mother antenatally in relation to allergy outcome in the baby is not clear.

In T07005 we hypothesised that maternal avoidance of dietary egg from early in the second trimester of pregnancy and throughout lactation would lead to a reduced incidence of egg allergy and associated allergic problems in babies born in high risk families where one or other parent was also allergic. This study highlighted that employing an avoidance diet was very difficult and only 16% of the mothers in the intervention group were able to sustain complete egg avoidance. Nevertheless in the intervention group ovalbumin specific IgG fell significantly and was correlated with significant reductions in

egg intake. Overall there was no significant effect of avoidance on any allergic outcome up to 1 year of age. There were complex interactions between maternal allergic status, egg intake and allergy outcome. Thus, if the mothers were allergic, reduced egg intake reduced allergy outcome in the infant. However, if the mother was non allergic a low egg intake was associated with an increased risk of allergy in the infant. Thus the key conclusion from this study was that attempting dietary avoidance does not achieve total elimination and overall in a whole population does not achieve any benefits compared with sustaining a normal diet. There was a suggestion that very high intakes of egg associated with high ovalbumin specific IgG by the time of birth was associated with a lower prevalence of allergy than where the intake of egg was in the moderate to low range with an equivalent lower ovalbumin specific IgG. This led to the hypothesis for the subsequent study T07033.

The second study investigated the role of maternal IgG antibody in modifying the foetal immune response to food antigens in relation to allergy outcome. This demonstrated that there were 2 routes of intrauterine transfer of allergen from mother to foetus. In the second trimester of pregnancy the predominant exposure was directly to allergen which passively transferred across the amnion into amniotic fluid and thereafter was swallowed by the foetus. Previously we had demonstrated mature immune responses in the foetal gut with a bias towards TH-2 responses suggesting that this route of exposure could be associated with sensitisation. In the third trimester of pregnancy active IgG transport across the placenta led to a combination of exposures either of allergen complexed with IgG or free or a combination of the 2. However, the pattern of exposure at this stage in pregnancy did not appear to impact on later allergy. Additional exposures to allergen occurred via maternal breast milk. 1 additional unexpected output from the study related to the ovalbumin employed for in vitro studies. Those obtained from Sigma were all contaminated with endotoxin and the endotoxin content had a significant impact on the in vitro cellular responses. This compromised the possibility of identifying whether specific IgG antibody against ovalbumin would modulate mononuclear cell responses in culture to ovalbumin.

T07044 was established to investigate the hypothesis that there is a bell shaped curve of allergic sensitisation and disease in offspring in relation to maternal exposure to allergen but that this will be modified by the maternal immune response to that allergen. 242 subjects were recruited into the study. A validated food frequency questionnaire has been employed during pregnancy at 24 and 38 weeks' gestation showing good reproducibility with food diaries in a 50 subject validation study and infants are being followed through the first months of life to establish which have developed evidence of allergic sensitisation and disease. Blood samples have been collected from the mothers through pregnancy, cord blood and from the infants postnatally. Unfortunately funding for the study was not extended at the end of Phase I which means that follow up will be incomplete. Levels of proteins from cows' milk and egg measured at 24 and 38 weeks' gestation correlated well with one another as did the dietary intakes of egg and milk at

these 2 time points. However, there was no correlation between levels in the blood and the amount of milk and egg consumed by the mothers in the previous month. However, this is not surprising as the amounts in blood are only representative of what has been eaten in the previous 2 to 6 hours. Levels of antibodies to milk and egg proteins correlated with one another at the 2 time points but were independent of dietary intake. Ostensibly this might appear disappointing but will allow a discrimination between the effects of the food protein intake itself and of the potential effects of transfer of antibodies to these foods from mother to baby. It is too early to make any comments about effects on outcomes.

An additional component of this study is the detection of cellular immune responses to the food proteins from the cord blood with particular focus on tissue homing molecules to establish whether these influence the clinical manifestations of allergic sensitisation. This component of the study is supported by a PhD fellowship from the Agency and is the means by which the study will still achieve at least some of its original objectives.

Investigation of the Role of Maternal Experience of Dietary Antigen on the Subsequent Immune Status of their Offspring

Dr Bevis Miller
University of Bristol

Project team
Dr G Corfield, Dr MJ Kenny, Dr P Jones, Dr K Haverson, M Bailey and C Stokes.

Project number: T07026

Start date: March 2002 **End date:** August 2006

Rationale for Funding the Research

It is considered that a number of environmental and genetic factors (other than atopic status) may influence individual susceptibility to food allergy. A better understanding of the critical factors involved in susceptibility and onset of allergy to food proteins was required in order to underpin possible future preventative or immunomodulatory strategies. The role of in utero exposure, maternal and weaning diets in particular needed further investigation. Research proposals were therefore invited to determine how age and route of exposure influences the development of sensitisation and food allergy.

Study Design and Aims

The objective of this project was to identify in an animal model whether exposure to antigen, antibody or immune complex (where the antibody is bound to its antigen) at birth affected subsequent immune development. The pig was chosen as the animal model since pigs in contrast to the human, are born devoid of any maternal antibody or maternally derived dietary antigen since the placenta of the pig lacks the ability to transfer large molecules such as proteins. As such, by exposing the pig at birth it is possible to mimic the in utero exposure which occurs in humans. The pig therefore offers an almost unique opportunity (not available in rodent models) to manipulate very early immune exposure.

Detailed information on the effects of very early exposure (in utero or at birth) to either antigen or antibodies will add to the body of evidence to inform any discussion both by the Agency and clinicians concerning the COT advice.

Pigs were removed from a commercial farm at birth (prior to suckling their dams) and transferred to the University of Bristol Specific Pathogen Free Intensive Care Unit for piglets. They were then cared for individually and fed hourly artificial milk. Immediately upon arrival within the unit, pigs were given orally either physiologically buffered saline (control group) or a solution containing ovalbumin (egg allergen), anti-ovalbumin antibody or a complex of the 2. The anti-ovalbumin antibody, having previously been prepared by

either injection (hyperimmune) or feeding with ovalbumin (tolerant), to a separate group of pigs and subsequent collection of their sera. The pigs are defined as hyperimmune because they respond to injected antigen in contrast to the tolerant group who are orally tolerant following feeding and thus fail to respond to injected antigen.

At 16 days of age the isolator reared piglets were exposed to ovalbumin either by injection or by feeding and their subsequent immune response assessed. The aim being to determine whether the early immune exposure had affected the way the piglets at 16 days, responded to antigen presented either systemically (injection) or at the gut mucosa (feeding). 2 methods of antigen exposure were utilized given that it is well established that immune responses at a mucosal surface can be significantly different from systemic challenge. Several markers of immune function were monitored including serum antibody responses, phenotypic analysis and culture of isolated immune cells from the gut, spleen and blood along with both conventional histology and immunohistochemistry of the small intestine.

Results and Conclusions

The results from the immune function assays clearly indicated that oral exposure at birth to 1g of ovalbumin, suppressed any subsequent immune response when exposed to ovalbumin whether by injection or orally at 16 days of age. Lower doses of 100mg or 1mg had respectively only a marginal or no affect. The conclusion being that the higher level of early exposure to ovalbumin induces oral tolerance in neonatal pigs. No affects of antibody (whether derived from hyper-immune or tolerant pigs), given alone at birth on subsequent immunity were observed. It is important to note that these antibodies were derived from non-atopic pigs who had no observable clinical symptoms when fed ovalbumin. Serum from atopic pigs may be significantly different from non-atopic pigs and thus any effect upon immune development when given to neonatal pigs may also be different. Arguably an atopic pig model would be a better model for human allergy. Pigs given complexes (antibody plus ovalbumin) at birth showed minimal responsiveness when subsequently challenged either orally or by injection with ovalbumin, indicating that oral tolerance may have been induced.

The results inform the discussions about the importance of timing, route and dose of exposure to allergen in the acquisition of sensitisation to food proteins, since they infer that neonatal antigen exposure induces oral tolerance. However, caution must be exercised since the pig model used may not reflect the response of children from allergic human mothers. The observations should therefore be confirmed using serum from sows made atopic and it established whether exposure to antigen at birth also induces oral tolerance in these animals.

Peanut Allergy: Routes of Pre-Natal and Post-Natal Exposure

Professor Gideon Lack
King's College London

Project team
Dr Adam Fox

Project number: T07043

Start date: September 2004 **End date:** September 2005

Rationale for Funding the Research

Results from previous Agency funded studies have suggested that dermal exposure may, in some circumstances, be a route of sensitisation to food allergens. There was a need to further understand the importance of routes of exposure other than oral ingestion, for the development of sensitisation to food allergens in both children and adults. This information would improve our understanding of the route and process by which sensitisation may occur and make it possible for the Agency to provide more complete advice to consumers. Proposals were therefore invited to investigate the importance of routes of exposure, other than by oral ingestion, on the development of sensitisation to food allergens.

Study Design and Aims

Over 90% of peanut allergic children react on their first known exposure. The route by which sensitisation occurs is unclear. Much work has focused on maternal consumption of allergen (during pregnancy or lactation) yet interventional studies have failed to demonstrate any benefit of dietary elimination. Recent data demonstrates that rashes and the topical application of peanut oil containing preparations to the infant's skin are risk factors for the development of peanut allergy. This suggests that this low dose cutaneous exposure is a likely route of sensitization. However, consumption of peanut containing foods by household members, especially during the child's first year of life, is another important source of environmental peanut exposure.

Our study utilised a validated retrospective dietary questionnaire in a cohort of children with suspected allergy and age-matched controls to investigate the role of the infants' environmental peanut exposure that results from household peanut consumption. We compared household peanut consumption in the first year of life in children with peanut allergy to normal children and high risk children (egg allergic) who are not peanut sensitised. Recall bias regarding peanut consumption by families whose child was peanut allergic was avoided by obtaining data before such a diagnosis was suspected. This

required administration of the questionnaire to children with difficult eczema or other food allergies who had not reacted to peanuts in the past. After information on peanut consumption had been obtained, the data was only utilised if later allergy testing to peanut reached values that were >95% positive predictive values for clinical allergy.

Results and Conclusions

Median weekly household peanut consumption in the peanut allergic cases (n=126) was 77.2g as compared with 29.1g in the normal controls (n=150) and only 8.1g in the egg allergic controls (n=160). Pair-wise comparisons between the 3 groups each gave significant differences with a p-value <0.0001. Differences in maternal peanut consumption during pregnancy and lactation are less significant and become non-significant after adjusting for other dietary factors.

These results suggest that increased exposure to environmental peanut promotes allergy whilst low levels may be protective. This supports our hypothesis that peanut sensitization occurs as a result of environmental exposure through cutaneous or inhalational routes rather than from maternal or infant allergen consumption. If sensitization is occurring through environmental exposure, this has important implications for current Department of Health guidance and future allergy prevention studies.

Characterisation of the Immune MechanismsInvolved in the Induction of Oral Tolerance to Peanuts in Children

Professor Gideon Lack
King's College London

Project team
Dr Victor Turcanu, Dr George Du Toit and Dr Alick Stephens

Project number: T07049

Start date: July 2007 **End date:** July 2012

Rationale for Funding the Research

This project was funded following an approach from an existing T07 research contractor seeking Agency collaboration with the US NIH's Immune Tolerance Network (ITN) on a major clinical intervention study on the induction of oral tolerance to peanut in children. The Agency considered that this was a unique opportunity to gain access to an important clinical trial in an area of direct relevance to current Agency policy needs and research interests to understand at immunological level, what factors are important in determining/regulating the development of sensitisation, allergy and tolerance to peanut in children. Improving our understanding in these areas could lead to the identification of potential preventative or immunomodulatory strategies and could directly inform the Agency's advice to consumers regarding dietary exposure to food allergens during early childhood.

Study Design and Aims

Peanut allergy (PA) affects about 1 in 70 children in the UK despite widespread peanut avoidance in the first years of life. However, it is not clear whether children should avoid peanuts to escape sensitisation or should rather eat peanuts to induce early oral tolerance and thus prevent PA. Indeed, there is evidence that the prevalence of peanut allergy is decreased in countries where children are fed peanut-containing foods beginning at an early age. Indeed, clinical observations from countries in Southeast Asia, Africa or from Israel, where peanuts are consumed in high amounts in different snack forms during infancy, suggest the rate of peanut allergy to be relatively low in comparison with countries where peanut consumption is avoided during the first years of life, such as the UK.

We are conducting at King's College London a randomized controlled trial, funded by the National Institutes of Health (USA), in which 480 4-10 month old children at high risk for peanut allergy (PA) (as predicted by moderate-to-severe eczema or egg allergy) will either eat peanut-containing snacks until age 5 or, conversely, will avoid peanuts and will just be observed. We expect peanut-eating children will show a significant decrease in PA. Under

Agency funded project T07049, we are utilising blood and serum samples that are being collected from children participating in the trial, to investigate (longitudinally) the immunological mechanisms that underpin the acquisition of oral tolerance to peanut in children. Specifically, we shall monitor peanut-specific T and B cell responses, regulatory T cells and antibody isotypes during the trial.

The expected outcome of this study is the identification of the role of early exposure to peanuts in the induction of tolerance and allergy respectively to peanuts and also the characterisation of the immunological mechanisms of prophylactic oral tolerance induction. This should provide the FSA with the scientific information necessary for designing new approaches to prevent food allergies and would provide a scientific basis for policies and guidance on food consumption and exposure to food contaminants, especially during childhood.

Results and Conclusions (to date)

During the months passed since the beginning of the trial we have focused on recruiting the participants required for the study (480 participants aimed to be recruited between 01/01/2007 and 31/12/2008).

We have achieved our planned recruitment targets so far; thus, as of 26 September 2007, we had recruited 205 participants into the trial and we collected blood from all of them (average volume 7.6ml, range 0.75-10ml).

On average, the number of peripheral blood mononuclear cell (PBMC) number that we separated and frozen is 45 million and the plasma volume obtained is on average 3.1ml. Considering that for the assays that we plan to carry out at King's College London we only require 6 million PBMC and 0.25ml plasma, this ensures that there will be no problems in performing them.

Randomised Controlled Trial of Early Introduction of Allergenic Foods to Induce Tolerance in Infants

Professor Gideon Lack
King's College London

Project team
Dr Michael Perkin

Project number: T07051

Start date: January 2008 **End date:** July 2014

Rationale for Funding the Research

It was recognised that although genetic predisposition plays an important role in atopy and susceptibility to the development of food allergy, there are other factors that influence whether a child will develop clinical allergy or tolerance. Of particular interest is the possibility that weaning practices may be of importance. Proposals were therefore invited to determine the factors, including weaning practices that influence the development of clinical allergy or tolerance to food proteins in infants.

Study Design and Aims

In the UK 6% of children under the age of 6 years will develop food allergies (FA), 25% eczema, 20% asthma and 10% allergic rhinitis (AR). Department of Health guidelines advise exclusive breast feeding (EBF) for the first 6 months and delayed introduction of allergenic foods. There is little evidence that this reduces allergic disease. Interventional trials of delayed weaning have consistently failed to reduce FA and atopy. Animal models and preliminary human data suggest that high dose oral tolerance to food proteins in early life may prevent allergic sensitisation. 3 separate studies suggest that prolonged EBF is a risk factor for developing atopic disease. The trebling of allergic disease since the 1970's has coincided with a two-thirds reduction in early weaning. Thus delayed weaning could promote FA and even other atopic diseases.

In this project we will conduct a randomized controlled study in infants to determine whether early weaning and exposure to food allergens (from 3 months of age) prevents the development of FA, eczema, asthma and AR. This study will provide an informed basis for future policy and advice on weaning practices in both atopic and normal infants in the UK.

The design of the study is for a randomized controlled trial of the early introduction of allergenic foods in a normal population. 3000 mothers will be recruited to participate antenatally with the expectation that 2500 infants will be eligible for randomization at 3 months of age. An anticipated 20% drop out by 3 years of age will yield 2 groups of 1000 infants.

Participants will be encouraged to breast feed exclusively until 3 months of age when half of the infants will be randomized to introduce a number of foods (egg, milk, wheat, soya, fish and peanut) into the diet under dietetic direction. The control arm will follow standard Department of Health weaning advice (exclusive breast feeding until 26 weeks of age) and no allergenic foods (cow's milk formula, egg, wheat, peanuts, tree nuts, seeds, fish and shellfish) before 6 months of age. Both the intervention and the control arms will be encouraged to breast feed for at least 6 months and we will follow the Department of Health Infant Feeding Recommendation that breast milk "should continue to be an important part of babies' diet for the first year of life".

Participants will be followed up until 3 years of age by which point the impact of the intervention on the primary outcome (food allergy) and secondary outcomes (eczema prevalence, inhalant allergen sensitization, atopic wheeze phenotype and combined allergy prevalence) will be determined.

Potential Outcomes

The project is unique in that there have been no randomized interventional studies looking at the effects of early versus late weaning onto allergenic foods in general. This study would also provide an opportunity to investigate the safety and possible beneficial effects on growth and normal development of early weaning.

A positive outcome with the successful induction of tolerance would have profound implications for weaning policy both nationally and internationally. In addition, a reduction in the number of children with allergies would, in turn, have a significant cost benefit for the administration of healthcare.

Annex 8

Publications Arising from T07 Projects Included in the Review (as of February 2008)

Project Code	Publications
T07023	B. Pereira, C. Venter, J. Grundy, C. B. Clayton, S. H. Arshad, T. Dean. (2005) **Prevalence of sensitization to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers.** Journal of Allergy and Clinical Immunology, 116, (4), 884–892. C. Venter, B. Higgins, J. Grundy, C. B. Clayton, C. Gant, T. Dean. (2006) **Reliability and validity of a maternal food frequency questionnaire designed to estimate consumption of common food allergens.** Journal of Human Nutrition and Dietetics, 19, (2), 129–138. C. Venter, B. Pereira, J. Grundy, C. B. Clayton, G. Roberts, B. Higgins, T. Dean. (2006) **Incidence of parentally reported and clinically diagnosed food hypersensitivity in the first year of life.** Journal of Allergy and Clinical Immunology, 117, (5), 1118–1124. B. Pereira, C. Venter, J. Grundy, C. B. Clayton, S. H. Arshad, T. Dean. (2005) **Prevalence of sensitisation to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers.** Journal of Allergy and Clinical Immunology, 116, (4), 884–892. T. Dean, C. Venter, B. Pereira, S. Arshad, J. Grundy, C. Clayton, B. Higgins. (2007) **Patterns of sensitization to food and aeroallergens in the first 3 years of life.** Journal of Allergy and Clinical Immunology, 120 (5), Pages 1166–1171. C. Venter, B. Pereira, K. Voigt, J. Grundy, C. B. Clayton, B. Higgins, S. H. Arshad, T. Dean. (2008) **Prevalence and cumulative incidence of food hypersensitivity in the first three years of life.** Allergy, 63, (3), 354–359. C. Venter, B. Pereira, K. Voigt, J. Grundy, C. B. Clayton, C. Gant, B. Higgins, T. Dean. (2007) **Comparison of open and double-blind placebo-controlled food challenges in diagnosis of food hypersensitivity amongst children.** Journal of Human Nutrition and Dietetics, 20, (6), 565–579.

T07025	J. S. A. Lucas, S. A. Lewis, J. Hourihane. (2003) **Kiwi fruit allergy: A review.** Pediatric Allergy and Immunology, 14, 420–428. J. S. A. Lucas, K. E. C. Grimshaw, K. Collins, J. O. Warner, J. Hourihane. (2004) **Kiwi fruit is a significant allergen and is associated with differing patterns of reactivity in children and adults.** Clinical & Experimental Allergy, 34, 1115–1121.
T07026	• Not applicable
T07032	S. S. Tay, A. T. Clark, J. Deighton, Y. King, P. W. Ewan. (2007) **Patterns of immunoglobulin G responses to egg and peanut allergens are distinct: ovalbumin-specific immunoglobulin responses are ubiquitous, but peanut-specific immunoglobulin responses are up-regulated in peanut allergy.** Clinical and Experimental Allergy, 37, (10), 1512–1518.
T07033	G. H. Vance, K. E. Grimshaw, R. Briggs, S. A. Lewis, M. A. Mullee, C. A. Thornton, J. O. Warner. (2004) **Serum ovalbumin-specific immunoglobulin G responses during pregnancy reflect maternal intake of dietary egg and relate to the development of allergy in early infancy.** Clinical and Experimental Allergy, 34, (12), 1855–1861. G. H. Vance, C. A. Thornton, T. N. Bryant, J. A. Warner, J. O. Warner. (2004) **Ovalbumin-specific immunoglobulin G and subclass responses through the first 5 years of life in relation to duration of egg sensitization and the development of asthma.** Clinical and Experimental Allergy, 34, (10), 1542–1549. G. H. Vance, S. A. Lewis, K. E. Grimshaw, *et al.* (2005) **Exposure of the fetus and infant to hens' egg ovalbumin via the placenta and breast milk in relation to maternal intake of dietary egg.** Clinical and Experimental Allergy, 35, 1318–26.
T07034	J. Turke, C. Venter, T. Dean. (2005) **Maternal experiences of peanut avoidance during pregnancy/lactation: An in-depth qualitative study**. Pediatric Allergy and Immunology, 16, (6), 512–518 T. Dean, C. Venter, B. Pereira, J. Grundy, C. B. Clayton, B. Higgins. (2007) **Government advice on peanut avoidance during pregnancy – is it followed correctly and what is the impact on sensitisation.** Journal of Human Nutrition and Dietetics, 20, 95–99.
T07035	J. Hourihane, R. Aiken, R. Briggs, L. Gudgeon, K. Grimshaw, A. DunnGalvin, S. Roberts. (2007) **The impact of government advice to pregnant mothers regarding peanut avoidance on the prevalence of peanut allergy in United Kingdom children at school entry.** Journal of Allergy and Clinical Immunology, 119 (5), 1197–1202.

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T07038	J. S. A. Lucas, S. A. Lewis, J. B. Trewin, K. E. C. Grimshaw, J. O. Warner, J. Hourihane. (2005) **Comparison of the allergenicity of Actinidia deliciosa (kiwi fruit) and Actinidia chinensis (gold kiwi).** Pediatric Allergy and Immunology, 16, (8), 647–654. J. S. A. Lucas, N. J. Nieuwenhuizen, R. G. Atkinson, E. A. MacRae, S. A. Cochrane, J. O. Warner, J. Hourihane. (2007) **Kiwifruit allergy: actinidin is not a major allergen in the United Kingdom.** Clinical and Experimental Allergy, 37, (9), 1340–1348.
T07040	D. McCann, A. Barrett, A. Cooper, D. Crumpler, L. Dalen, K. Grimshaw, E. Kitchin, K. Lok, L. Porteous, E. Prince. (2007) **Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial**. The Lancet, 370, (9598), 1560–1567.
T07041	• Not applicable
T07042	S. S. Tay, A. T. Clark, J. Deighton, Y. King, P. W. Ewan. (2007) **T cell proliferation and cytokine responses to ovalbumin and ovomucoid detected in children with and without egg allergy.** Clinical and Experimental Allergy, 37, (10), 1519–1527.
T07043	• Not applicable
T07044	• Not applicable
T07045	• Not applicable
T07046	• Not applicable
T07048	• Not applicable
T07049	• Not applicable
T07051	• Not applicable

Annex 9

Glossary and Abbreviations[5]

Allergen: Substance, usually a protein or glycoprotein, capable of inducing an allergic response.

Allergy: Adverse health effects resulting from a specific immune response.

Anaphylaxis: An immediate (IgE mediated) reaction to a foreign substance, which in severe cases can be generalised and life threatening.

Antibody: Immunoglobulin which is specific for an antigen or allergen.

Antigen: Substance recognised by the immune system.

Asthma: Chronic inflammatory disease of the air ways which renders them prone to narrowing. The symptoms include paroxysmal coughing, wheezing, tightness and breathlessness. Asthma may be caused by an allergic response or may be induced by non-immunological mechanisms.

Attention deficit hyperactivity disorders (ADHD): Condition characterised by inattentiveness, overactivity and/or impulsiveness.

Atopic dermatitis: Disease of the skin characterised by itching and dry and lined skin.

Atopy: Predisposition to IgE production associated with allergy to several common allergens.

Avidity: Strength of antibody binding.

Coeliac disease: Disease characterised by damage to the small intestinal wall due to intolerance of gluten, a protein present in cereals, such as wheat, rye and barley.

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT): Committee composed of independent experts, which advises government on the human health risk of chemicals in food, consumer products and the environment.

CST: Chief Scientist Team of the Food Standards Agency.

Cytokine: Mediators produced by a variety of cell types, and which influence immune and inflammatory responses in a variety of ways.

[5] This glossary contains explanations of terms used in the text not exact definitions.

Dermatitis: Inflammation of the skin.

DH: Department of Health.

Double-blind placebo-controlled food challenge (DBPCFC): An *in vivo* test in which the patient and doctor do not know which food is being tested until after the tests and the recording of responses have been completed. Often regarded as the 'gold standard' for testing for allergenicity.

DNA: Deoxyribonucleic acid.

ELISA: Enzyme linked immunosorbent assay.

Epitope: Peptide sequence within an antigenic molecule which is recognised by the immune system (either lymphocytes or antibodies).

FABIC: Food Additives and Behaviour in Children. A Working Group established to consider the feasibility of conducting further definitive research on the subject of the link between food and hyperactive behaviour.

Food additive: Substance added to food to facilitate some part of the processing or manufacture of the foodstuff or to impart a particular characteristic; they can be classified according to the purpose for which they are used, e.g. food colours, antioxidants, acidity regulators.

Food allergy: Adverse reactions to food, mediated by immunological mechanisms.

Gluten: Protein present in cereals such as wheat, intolerance to a component of which is a characteristic of coeliac disease.

Glycoprotein: A molecule that consists of a carbohydrate plus a protein. Glycoproteins play essential roles in the body, in the immune system almost all of the key molecules involved in the immune response are glycoproteins.

Histamine: Decarboxylation product of the amino acid histidine. It is an important inflammatory mediator.

Hyperactivity: A general term used to describe non-specific behavioural difficulties, including impairment of learning, memory, motor skills, language, control of emotional responses and sleep patterns. There is no single test for diagnosing such behaviour.

Immunoglobulin (Ig): A member of a family of proteins from which antibodies are derived. There are 5 main classes in humans known as IgM, IgG, IgA, IgE and IgD.

IgE: 1 of the 5 main classes of immunoglobulin. IgE is involved in allergy and anaphylaxis as well as protecting against intestinal parasites. IgE mediated hypersensitivity is characterised by the rapid release of mediators such as histamine.

IgG: 1 of the 5 main classes of human immunoglobulin and is the most abundant.

Immunoblotting: A technique for analysing and identifying protein via antigen-antibody specific reactions.

Incidence: The number of new cases of a disease that occur during a particular period of time in a defined population.

Intolerance: General term for a reproducible adverse reaction often to food and food ingredients. In this report, the term embraces both allergic and nonallergic reactions.

Langerhan cells: Phagocytic dendritic cells found in the epidermis. They can migrate from the epidermis to regional lymph nodes via the lymphatic system. In the lymph node they differentiate into dendritic cells.

Lymphocyte: A specialised white cell with a variety of immunological functions, including antibody production (B lymphocytes) and cell mediated reactions (T lymphocytes). T lymphocytes also have a regulatory effect on antibody production.

MAFF: Ministry of Agriculture Fisheries and Food.

Mast cells: Cells found predominantly in connective tissue, although a specialised population of mast cells is found in mucosal sites (e.g. the gut). Following degranulation, mast cells release preformed and newly synthesised mediators of inflammation, including histamine.

Open food challenge (OFC): In the context of adverse reactions to food, challenging the patient with the food suspected to cause the adverse reaction, without any attempt to hide the nature of the challenge from the observer or the patient.

Peanut: Nut from a herbaceous plant. It is also known as the groundnut or monkey nut, botanical name Arachis hypogaea. It is a member of the Leguminosae family and thus related botanically to peas and beans, rather than tree nuts such as brazil, hazel or almond. Used in a number of foodstuffs and also used to produce peanut oil.

Peanut oil: Also known as arachis oil. Used in foods and other products such as skin creams.

Pharmacological: Concerned with the action of drugs.

Prevalence: Total number of cases of a disease in existence at a certain time in a designated population (including new and old cases).

RCU: Research Co-ordination Unit of the Food Standards Agency.

Rhinitis: Inflammation of the nasal passages, resulting in runny nose.

ROAME: Rationale, Objectives, Appraisal, Monitoring, Evaluation. A system of research management.

SCF: Stem cell factor is a glycoprotein that plays a key role in hematopoiesis acting both as a positive and negative regulator, often in synergy with other cytokines.

Serotonin: Vasoactive decarboxylation product of the amino acid tryptophan, also known as 5-hydroxytryptamine.

Sensitisation: The stimulation of allergic antibody production usually by an initial encounter with a specific allergic substance. Synonymous with primary response.

Skin prick test (SPT): A clinical test of allergic reactivity, commonly used in allergy clinics.

Th1: T helper lymphocytes type 1. Subgroup of T lymphocytes which produce cytokines such as IFN-γ. In general, their actions antagonise the IgE and allergic responses.

Th2: T helper lymphocytes type 2. Subgroup of T lymphocytes which produce cytokines e.g. interleukins that promote IgE production and allergic responses.

T lymphocytes (T cells): Thymus-dependent lymphocytes which, amongst other functions, help B lymphocytes (B cells) during immunological responses and provide protection from intracellular microbial infection.

Urticaria: An itchy rash which results from inflammation and leakage of fluid from the blood into the superficial layers of the skin in response to various mediators. Synonyms are 'hives' or 'nettle rash.'

Annex 10

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