

Review

Food allergy – science and policy needs – The UK Food Standards Agency Research Programme

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ABSTRACT

Food allergy is a significant health issue in the UK, affecting between 1 and 2% of adults and 5 and 8% of children. The UK Food Standards Agency seeks to ensure the safety of food allergic consumers by providing them with information and guidance on food choices. Since 1995, with the aim of addressing important policy issues and improving the quality of the support and guidance available for food allergic consumers, the Agency (and before that the Ministry of Agriculture, Fisheries and Food), has had a programme of research dedicated to investigating the causes and mechanisms of food allergy and delivering benefits for UK consumers. In this paper, we outline some of the major scientific challenges that the programme has sought to address. We reflect on how the findings have been used as a basis for the development of sound, evidence-based policy and advice for UK consumers, and the current direction of research being supported by the programme.

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1. Introduction

This article will focus exclusively on food allergy, and it is therefore important to distinguish this from food intolerance. By definition, allergy is a manifestation of an immune response, and food allergy may be characterised as adverse immune reactions to foods. In contrast, food intolerance can be defined as reproducible adverse reactions, mediated via non-immunological mechanisms, following dietary exposure to a food or food ingredient. Food intolerance

may be associated, for instance, with a specific enzyme deficiency (Kimber and Dearman, 2001). In common with other forms of allergic disease, food allergy develops in two stages. In the first of these, exposure to an allergen results in immunological priming and the acquisition of sensitisation. If the sensitised subject is exposed subsequently via the diet to the same inducing allergen, then an allergic reaction may be provoked.

Food allergy is an important health issue. In the UK and USA the prevalence of true food allergy among adults is commonly believed to be in the range of 1–2%, with the prevalence among infants being somewhat higher at approximately 5% (Helm and Burks, 2000; Rona et al., 2007; Branum and Lukacs, 2008). In these countries most cases of food allergy are associated with a comparatively small number of foodstuffs, specifically: cows' milk, hens'

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eggs, wheat, fish, shellfish, peanuts and tree nuts (Young et al., 1994; Sampson, 1988). However, it is clear that patterns of food allergy can change according to local dietary preferences, and that a wide variety of foodstuffs are able to cause allergic sensitisation in susceptible subjects (Hefle et al., 1996; Hourihane, 1998).

The symptoms of food allergy include nausea and vomiting, and abdominal pain, flatulence and diarrhoea. However, organ systems other than the gastrointestinal tract may be involved (notably the skin and respiratory tract), and occasionally severe, and potentially fatal, systemic reactions (anaphylactic shock) may be provoked (Sampson, 1999, 2000). Although there is considerable interest in the development of desensitisation strategies for food allergy (Meglio et al., 2008; MacDonald and Di Sabatino, 2009; Clark et al., 2009; Sicherer and Sampson, 2010), effective clinical management presently remains based on avoidance of the relevant food(s).

Most food allergy is associated with IgE antibody-mediated responses against the inducing food protein(s), although IgE-independent food allergy does occur. A detailed survey of the complex immunological mechanisms that serve to initiate and orchestrate allergic responses to food proteins is beyond the scope of this article, and recent reviews are available elsewhere (MacDonald and Di Sabatino, 2009; Sicherer and Sampson, 2010). It is relevant, however, to draw attention to the fact that the majority of individuals within the general population will tolerate a varied diet throughout their lives without manifesting a clinically discernible allergic reaction to food proteins. Moreover, even in susceptible individuals (commonly those with an atopic phenotype and a predisposition to mount IgE antibody responses), not all proteins encountered in the diet, and commonly only one or a small number, will elicit an allergic response. The normal situation, therefore, in unaffected subjects is that food proteins are tolerated without the acquisition of allergic sensitisation, and there remains considerable interest in characterising how such tolerance is developed and maintained, because this may provide clues for the design of effective therapeutic and/or prevention strategies (Strobel and Mowat, 1998, 2006; Mowat, 2003; Chehade and Mayer, 2005). It is important to appreciate, however, that in immunological terms tolerance to food proteins is not absolute. It would appear, in fact, that the production of IgG antibodies is the normal immunological consequence of regular exposure to dietary proteins in both adults and children (Barnes, 1995; Kimber and Dearman, 2002). An important and intriguing question in understanding why and how food allergy develops is, therefore, under what circumstances does a dietary protein elicit an IgE antibody response resulting in the acquisition of sensitisation. Although many aspects of this question remain unanswered, it is possible to generalise insofar as the development of sensitisation is known to depend upon: (a) the nature of the food and the presence of proteins that are potentially able to elicit IgE antibody responses (potentially allergenic proteins), (b) the inherent susceptibility of the individual, and in particular, the possession of an atopic phenotype, and (c) the conditions (including for example magnitude, duration, route, timing and context) of exposure. The importance of the latter is illustrated by the fact that a subject borne of two atopic parents with food allergy will be predisposed themselves to the development of food allergy, but will not necessarily do so and not necessarily to the same dietary proteins. The protein(s) to which a susceptible subject will respond and acquire sensitisation is a complex function of the timing and conditions of encounter (Kimber and Dearman, 2002). The broad factors that affect the acquisition of sensitisation to food proteins are illustrated in Fig. 1.

While Fig. 1 identifies the variables that can impact on the development of sensitisation and the elaboration of IgE antibodies specific for dietary protein(s), it is important to appreciate that sensitisation (as defined by the serological identification of food protein-specific IgE antibody) does not necessarily translate into

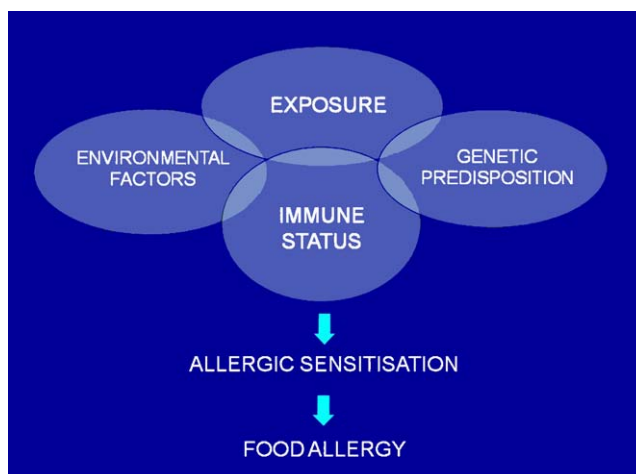


Fig. 1. Factors that influence the acquisition of sensitisation to food proteins that may translate into food allergy.

clinical food allergy (Sicherer and Sampson, 2010). It is currently unclear what factors act to prevent the development of clinical (symptomatic) food allergy in otherwise sensitised individuals and this is a significant area of research interest. In addition, it is not clear what factors determine the severity of food allergic reactions. What is known is that the threshold of exposure for elicitation of a food allergic reaction during challenge of food allergic subjects, and the severity of those reactions, differ between individuals, and vary with time in the same individual (Summers et al., 2008; Taylor et al., 2010).

Against this background of incomplete knowledge, there is a continuing need for research to address these and other important scientific issues relating to food allergy. Improved understanding is vital to providing a sound basis for the development of therapeutic and/or preventative strategies for food allergy, as well as for the formulation of sound guidance for consumers and other stakeholders.

2. UK Food Standards Agency's Research Agenda

The Food Standards Agency (hereafter referred to in this paper as 'the Agency') has a remit to protect the health of UK consumers in relation to food by helping consumers make informed choices about the foods they purchase and consume. In the case of food allergy, this is achieved by negotiating and implementing legislation on the labelling of allergenic food ingredients, as well as by providing guidance and best practice advice to food businesses and enforcement bodies to improve the control and management of food allergens through the food supply chain, and by providing advice to food allergic consumers themselves. The Agency is committed to ensuring that its policies are based on sound evidence and the best possible information. Research is commissioned in order to address particular areas of policy need, with the aim of informing the guidance and advice that the Agency gives to food businesses and to consumers, both those that have already developed a food allergy and also those consumers who are at risk of developing a food allergy.

The Agency's Food Allergy and Intolerance Research Programme was established in 1995 by the Ministry of Agriculture, Fisheries and Food, originally to investigate the causes and mechanisms of severe food allergy, concentrating particularly on peanut and tree nut allergy and the latter stages of food allergic disease, when sensitisation has already developed into clinical allergy. However, more recently the Programme has evolved to focus on two other areas where existing knowledge is poor and where the Agency consid-

ers that advances in the science could deliver significant public health benefits. The first of these is to establish the current prevalence of food allergies in the UK, including whether, and to what extent, the prevalence is increasing, particularly in childhood when many food allergies tend to develop. The second is the identification and characterisation of factors (both genetic, and environmental or dietary) that might influence the development of sensitisation and clinical allergy to food allergens, so as to identify those at greatest risk of developing food allergy. Most recently the Programme has been focusing on the early life environment and, in particular, on the possible influences of dietary and non-dietary exposures to food allergens on the mechanisms underlying the acquisition of tolerance to allergenic foods and on the timing of that first exposure. Some of the specific areas on which the Programme has focused are summarised and discussed below, and in particular, with respect to how they have advanced scientific knowledge and informed Agency policy. The studies that have been funded by the Agency are presented and discussed in the context of other relevant research but the discussion is not intended to represent a comprehensive review of food allergy research more generally, nor is it an in depth review of the mechanisms of food allergy.

3. Highlights of the Agency's Food Allergy Research Programme

3.1. *The true prevalence of food allergy in the UK*

There is no doubt that since the Second World War in Western Europe and the USA, there has been a substantial increase in the prevalence of atopic disease and asthma (Strachan, 1989; Burney et al., 1990; Kimber, 1998; Anderson et al., 2004; Latvala et al., 2005). It has been assumed, but not definitively proven, that during the same period there has been a comparable generalised increase in the prevalence of food allergies within 'westernised' societies (Sicherer and Sampson, 2007). Nevertheless, there remains a need to monitor the incidence and demographics of food allergy in order that changes in susceptibility and the emergence of new food allergies can be identified, possible causes investigated and appropriate advice given to consumers. An illustrative example of where this has been of importance recently in the UK is in the context of considering the possible impact of Government advice issued in 1998 to atopic mothers regarding the avoidance of peanuts and peanut food products during pregnancy and lactation, and delayed introduction into the diet of these infants. One of the questions addressed through two studies in the Agency's research programme has been whether introduction of this advice, following recommendations made in a 1998 report by the independent Committee on Toxicity (COT, 1998), had impacted positively or negatively on the prevalence of peanut allergy in the UK.

The first of these studies (Hourihane et al., 2007), was a cohort study carried out in Manchester on children born after the 1998 COT advice on peanut avoidance, in which maternal dietary consumption was assessed retrospectively during pregnancy and breastfeeding, and subsequent rates of sensitisation and (oral challenge proven) allergy to peanuts were established prospectively in the children at age 3–4 years. This study indicated a probable rise in prevalence of peanut allergy among 3–4 year old children born after, compared with before, the 1998 advice was issued (1.8% (Hourihane et al., 2007) compared with 0.5% (Tariq et al., 1996)). However, it was demonstrated that this difference, if indeed real, was not any result of the advice itself because few of those mothers whose children developed peanut allergy had been atopic themselves and only one had actually avoided peanuts successfully (Hourihane et al., 2007). The second study was a similar study car-

ried out on a whole population prospective birth cohort on the Isle of Wight, in which maternal diet was assessed prospectively during pregnancy and breastfeeding in relation to allergy outcomes in the children at age 2 years. The two studies used the same specific questions to ask mothers about their peanut consumption/avoidance behaviour during pregnancy and breastfeeding. This second study found no evidence of a change in rates of sensitisation to peanut among 3 year old children (Dean et al., 2007), and comparison with previous cohorts drawn from the same geographical location using similar methodology and endpoint measurements indicated no significant change in peanut allergy rates in 2001–2002 compared with 1989, although there was a slight increase in the mid-1990s (Venter et al., 2010). Together, these data indicate that it is unlikely that the 1998 COT advice resulted in any significant change in the prevalence of peanut allergy in UK children. These studies also demonstrated that the overall rate for the current prevalence of peanut allergy in UK children is likely to lie somewhere between 0.2 and 1.8% (COT, 2008). The COT considered evidence on prevalence of food allergy in children, together with other evidence on the routes and timing of exposure when reviewing the advice it had previously issued on exposure to, or avoidance of, peanut (see later). Revised advice to consumers has subsequently been issued by the UK Government, taking account of COT's conclusions, and is available at <http://www.food.gov.uk/safereating/allergyintol>.

However it was also clear from these two studies that the original advice may not have been disseminated fully, or followed accurately by mothers. Thus, in one study 65% of women reported that they avoided peanut during pregnancy regardless of their own or their family's history of allergic disease. Of those who said they avoided peanuts, this avoidance may not have been absolute in all cases, with avoidance being only of food products obviously containing peanuts (Dean et al., 2007). In the other study, while many women recalled being given the advice, again uptake of the advice was not linked with atopic status and the majority of mothers only reduced intake of peanuts and did not completely avoid such foods (Hourihane et al., 2007). It is difficult to compare the reported rates of peanut sensitisation and peanut allergy in these two studies funded by the Agency with the existing published literature because of the differing methodologies used in the literature for the determination of clinical allergy and sensitisation. In particular, not all studies have based their derivations of allergy prevalence on the results of food challenges which are the gold standard for diagnosis and which were used in the Agency funded studies. The differing ages of the children in the cohorts studied and the differing geographic locations for the studies also complicate the drawing of comparisons. To address the issues of varying methodologies and criteria in the existing literature, the Agency has separately funded a major prospective study of the prevalence of individual food allergies among UK children, using a series of whole population cohorts recruited on the Isle of Wight and using gold standard methodologies to determine sensitisation and clinical allergy to foods among the children. That study has delivered robust data on the prevalence of allergies to all of the main allergenic foods across the full age range of children from birth to 16 years of age (Pereira et al., 2005; Venter et al., 2006, 2008), which will provide an important baseline for comparison with future UK estimates. Importantly it also demonstrated that rates of perceived food allergy amongst children in the UK are much higher than actual rates (Venter et al., 2008). This underlines the importance of seeking a proper diagnosis and appropriate dietary advice so that diets are not restricted unnecessarily, as this could impact on growth and nutrition.

Most recently, the Agency has provided matched funding for a large European Union-funded research project on the prevalence of food allergy, which includes a work-stream to determine the rates of food allergy in large prospective birth cohorts of children in a number of countries across Europe, using standardised method-

ologies and diagnostic criteria (Keil et al., 2010). The results from this work are likely to be published in 2011.

3.2. Impact of the introduction of new foods into the national diet

As highlighted above, there are certain foods that are frequently associated with food allergy. It is clear, however, that the particular foods commonly implicated as allergens are a reflection of the national diet and food preferences (Hourihane, 1998). The inference is that the introduction into the diet of new foods might be associated with the emergence, over time, of an increasing incidence of sensitisation and potentially allergy to proteins in those foods. Whether and how this occurs is of interest to the Agency because, as the UK food regulator, it is responsible for ensuring that new foods introduced into the UK market do not present any food safety risks, including risks of allergenicity. One interesting opportunity to test this hypothesis has been available recently in the UK. Kiwi fruit (*Actinidia deliciosa*), or Chinese gooseberry, is native to Southern China, but was first cultivated commercially in New Zealand. Kiwi fruit entered the UK diet gradually from the early 1970s. The Agency commissioned research to explore the significance, characteristics and demographics of kiwi fruit allergy in the UK in order to inform consumer advice and policy. This was accomplished using questionnaires completed by nearly 300 people with self-reported kiwi fruit allergy, followed by laboratory investigations on participants to characterise their kiwi allergies including skin prick testing, specific IgE measurement from serum samples and, where appropriate, oral challenges.

The Agency funded research demonstrated that in the 1970s there was very little allergy to kiwi fruit, but reports became more common in the 1980s, predominantly in adults. This mirrors findings from Finland and France (Mattila et al., 2003; Rance et al., 2005) that kiwi fruit can become an important food allergen in EU countries. Allergy to kiwi fruit became more evident in children and young adults the 1990s. Reactions were generally mild in adults (tingling of the mouth and throat, sore mouth, and swelling of the lips) but were more likely to be severe in young children (wheeze, blue lips or collapse) (Lucas et al., 2004). It was found that people who had severe reactions to kiwi fruit on first exposure were likely to continue to have severe reactions and most of those people whose first reactions were mild, were likely to continue to have mild reactions. In a few cases reactions became more severe on repeated exposure to kiwi fruit. People developing kiwi fruit allergy, particularly children, were commonly found to have other co-existing allergies; some of these being cross-reactive allergies to fruits, tree pollen or latex, but others were to non-cross-reactive foods such as peanuts, tree nuts, milk, egg and grass pollen. Approximately one third of the allergic individuals have asthma, eczema or hay fever (Lucas et al., 2004). The study also suggested that the major kiwi allergen to which people react in the UK may be different to that previously described in other studies conducted elsewhere (Lucas et al., 2007).

Through this research, it is clear that allergies to new foods introduced into the diet may not become apparent immediately after introduction, and that if only mild reactions are seen initially, this does not necessarily mean that people will not develop severe reactions in future. The current strategies for the assessment of the safety of newly introduced foods includes their potential for cross-reactivity to known food allergens, but cannot detect novel allergenic proteins. If such novel allergenicity is to be detected and characterised, then clinical monitoring would be needed for many years after introduction, as consumption patterns of that food are likely to change significantly following its introduction into the diet and reactions might not necessarily become apparent immediately after introduction.

3.3. The role of IgG antibody in food allergy

The role of IgE antibody in the acquisition of allergic sensitisation to food proteins is well-established. However, and as indicated above, it is clear that in both allergic and non-allergic subjects, a consequence of dietary exposure to sufficient amounts of a food protein can be the production of IgG antibody. It remains unclear whether the levels of IgG antibody reactive with food allergens are higher, lower, or unchanged in sensitised subjects compared with those that are not sensitised (Firer et al., 1987; Hedvig et al., 2002; Shek et al., 2005). While it is clear that IgG antibodies do not themselves provoke reactions in food allergic patients, it remains a possibility that they are nevertheless influential immunologically. Of interest in this context is the fact that there is no clear correlation between the levels of allergen specific IgE antibody and clinical responsiveness. Whereas high concentrations of IgE antibody can predict clinical reactivity (Sampson and Ho, 1997; Sampson, 2001), the associations are not always strong and even subjects with relatively high levels of IgE antibody can be shown to tolerate challenge with the food to which they are sensitised. It was therefore considered important to investigate whether IgG plays a role in the pathogenesis of food allergy. One interesting possibility is that IgG antibodies compete for antigen with IgE antibodies, or in some other way impact negatively on the development of IgE-mediated reactions. If this were the case, then clinical reactivity could conceivably be a function of the relative levels of IgG and IgE antibodies reactive with an allergenic protein, and measurement of specific IgG antibodies might usefully inform characterisation of the likelihood of a reaction. To address this hypothesis, investigations were commissioned to determine whether and to what extent IgG antibodies affect allergic reactions to food in sensitised subjects, and whether, if that were the case, this might account for the sometimes poor correlation between IgE antibody levels and clinical symptoms.

Within these investigations, the patterns of IgE, IgG, and IgG sub-classes IgG1 and IgG4 reactivity were studied in children from the Addenbrookes hospital allergy clinic with either peanut or egg allergy, or children whose allergy had resolved. These food allergies were selected as they are both common in childhood, but differ in that while egg allergy resolves with age in the majority of children affected, peanut allergy is persistent in most cases. The findings demonstrated that food specific IgG is made by all children exposed to egg and peanut regardless of their allergic status (Tay et al., 2007). Furthermore, there were no clear correlations between levels of specific IgG, specific IgG sub-classes, or the ratio of specific IgE/IgG and allergic status. It was concluded that production of IgG is likely to be a normal physiological response to the ingestion of the particular food protein, regardless of allergic status.

From the results of this study, it was also clear that measurement of levels of food allergen specific IgG cannot be used in the diagnosis of peanut or egg allergy, and the likelihood is that the same is true of other types of food allergy. Nor can it be used in the prediction of the severity of reactions. This is relevant because there are a number of companies currently offering IgG based self-diagnostic allergy testing kits on a commercial basis and it is possible that consumers could decide to avoid certain foods on the basis of the results of such tests, when they are not in fact allergic to that food. As a result of this research, the Agency issued advice to consumers that such tests have not been validated and that anyone who suspects that they have a food allergy or food intolerance should seek advice from a qualified health professional. The report of the House of Lords Science and Technology Select Committee Inquiry on Allergy, published in 2007, also expressed concern that IgG antibody tests are being used to diagnose food allergy in the absence of stringent scientific evidence and recommended

that the use of such tests should not be endorsed until conclusive report of their efficacy has been established (House of Lords, 2007).

3.4. The role of T lymphocytes in food allergy

For the vast majority of antigens it is well established that the initiation of antibody responses is dependent upon T lymphocyte function in the form of T cell 'help'. Thus, antigen-specific CD4⁺ T helper (Th) cells support and guide the development of antibody production, and also play important roles in the long-term maintenance of antibody responses. There exists considerable heterogeneity among Th cells. Many functional subpopulations have been described, the most fully characterised of which are Th1 and Th2 cells that secrete discrete patterns of cytokines. For the development of IgE antibody responses, and the acquisition of allergic sensitisation, Th2 cells and their cytokine products (including interleukins [IL] 4, 5 and 13) are required (Mosmann et al., 1997; Kimber et al., 2002; Bohle, 2006; Veldhoen, 2009; Paul and Zhu, 2010). On this basis, the assumption is that both sensitised and non-sensitised subjects that are regularly exposed to a particular food, and to which they have mounted an IgG antibody response (this having been shown above to be a normal consequence of exposure), will have demonstrable antigen-specific Th cells. It has also been assumed that in food sensitised subjects those Th cells would be biased towards a Th2-type phenotype supporting the production of IgE antibody. To test these assumptions, and with the objective of more fully elucidating the nature of T lymphocyte responses to dietary antigens which might identify targets for the development of immunomodulatory strategies, research projects were launched by the Agency.

Preliminary *ex vivo* studies conducted as part of a wider Agency funded study of food allergy based on the long-term Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, provided indications that proliferative T cell responses from peanut allergic individuals are different to those from non-allergic subjects and from those in response to control antigens (Turcanu et al., 2003). Proliferation in response to culture with peanut antigen was more rapid among T cell samples obtained from peanut allergic individuals than those from non-allergic controls, and the T cells that proliferated differed in terms of their cytokine producing phenotype. Peanut-specific T lymphocytes from peanut allergic children tended to display a Th2 biased cytokine producing phenotype, and those from non-peanut allergic children tended to display a Th1 biased phenotype (Turcanu et al., 2003). These preliminary findings were confirmed and extended via a second more detailed study of T cell responses which used sera from peanut allergic, peanut sensitised, and non-peanut allergic (peanut tolerant) subjects to investigate the functional basis of the observed differences. The findings of these investigations indicated that the higher proliferative T cell responses in peanut allergic individuals compared with non-allergic individuals were most likely caused by the presence of peanut-specific IgE facilitating antigen presentation (FAP) in peanut allergic children (Turcanu et al., 2010). Furthermore, B cell responses (measured by peanut-specific IgE) and T cell responses to peanut antigens were shown to be correlated in peanut allergic individuals and un-correlated in non-allergic controls, or in response to control antigens. This suggests that B cell responses to allergens in peanut allergic individuals are on-going responses that are closely linked with allergen-specific T cell responses, possibly through the positive feedback circuit triggered by IgE-mediated FAP. This mechanism (FAP) could also explain the maintenance of the allergic response even in the presence of only low and occasional exposure to peanut protein.

These findings have revealed a significant role for IgE in the immunological maintenance of food allergy via FAP which could

be utilised as a target for potential immunotherapy techniques, as well as providing useful additional immunological endpoint measures for potential use in monitoring the immunological effect of future interventions for food allergy. These studies have also provided preliminary evidence that the proliferative T cell response seen in peanut allergic individuals are driven predominantly by skin-homing CLA⁺ memory T cells as distinct from gut homing memory T cells (Turcanu et al., unpublished observations). This is potentially important because it suggests that exposure to peanut through the skin might be a route of sensitisation (see also below).

3.5. Relevant routes of exposure for the acquisition of sensitisation to dietary proteins

Not unexpectedly, the assumption has been that the acquisition of sensitisation to food proteins results exclusively or largely from dietary exposure. However, this may not necessarily be the sole route of exposure that is effective for the acquisition of sensitisation. Sensitisation via the skin is a well known mechanism in the context of contact allergy and it is possible that skin contact with protein allergens from foods can also result in sensitisation that may translate into food allergy. In the case of peanut allergy, it is known that many reactions in children occur on first known consumption of peanut (Van Asperen et al., 1983; Hourihane et al., 1997), which raises the question as to whether sensitisation may have already occurred via a different route of exposure on a previous occasion.

If skin exposure can result in sensitisation to dietary proteins then clearly this is of some moment in the context of risk assessment, and in defining strategies and consumer/patient advice aimed at reducing opportunities for the development of sensitisation and ultimately prevention of food allergy itself. Perhaps even more importantly, it is possible that the route through which a food protein is first encountered may impact on whether the outcome is allergic sensitisation or tolerance. A series of Agency funded research studies in this area, building into an integrated package of research, have been commissioned over recent years in order to address the central question of whether and how exposure to food allergens via the skin might promote the development of sensitisation and allergy to those foods.

The major ALSPAC study of food allergy mentioned previously, found a clear link between the development of peanut allergy in the children and the presence of oozing, crusted rashes (an indication of moderate to severe eczema) during infancy (Lack et al., 2003). This, coupled with the finding that the majority of those infants had been administered creams containing *Arachis* (peanut) oil, led to the emergence of the hypothesis that exposure to peanut allergens through the skin could have promoted the development of peanut allergy and to labelling changes on creams containing these oils to highlight their peanut content. Subsequent experimental investigations were commissioned to establish more conclusively whether exposure to food allergens via the skin could result in sensitisation. Those rodent studies, conducted using both peanut and egg allergens, reported that sensitisation to peanut or egg proteins, and sometimes even anaphylactic type responses upon first oral exposure, could indeed be induced by contact with skin that had been abraded to represent eczematous skin, and possibly also with intact skin (Strid et al., 2004a). Furthermore, it was shown that contact via the skin could effectively prevent the later development of oral tolerance (Strid et al., 2004a, 2005). These same investigations also demonstrated a tolerising effect of early oral consumption of food allergens that is dose dependent, in that relatively low doses of peanut or egg allergen administered orally enhanced peanut-specific IgE responses to subsequent exposure to peanut in the presence of adjuvant subcutaneously, while higher doses resulted

in oral tolerance and inhibition of IgE responses (Strid et al., 2004b, 2005).

It is difficult to extrapolate these findings from rodent studies directly to the human situation. However, there are some parallels with results of a subsequent study that the Agency commissioned to investigate whether environmental (non-oral) exposure to peanut during infancy is associated with the later development of peanut allergy in humans. That study was a retrospective case–control study that compared environmental exposure to peanut during the first year of life in children subsequently diagnosed with peanut allergy and in two groups of controls—children with egg allergy (but not peanut allergy) who had been referred to the same allergy clinic, and children attending general paediatric clinics with non-allergic complaints. The study found that median weekly household peanut consumption during the first year of a child's life was very significantly higher in children who went on to develop peanut allergy (18.8 g) compared with those that did not (controls) (6.9 g/week) and compared to those who developed egg allergy (high-risk controls) (1.0 g) (Fox et al., 2009). Importantly, this relationship was independent of the child's own level of consumption of peanut suggesting that the higher risk of developing peanut allergy was linked with increased early environmental exposure to peanut rather than to oral consumption of peanut. While it is recognised that environmental exposure does not solely consist of exposure via the skin (inhalation routes and potentially very low level oral consumption potentially also being a consequence of environmental exposure to food allergens in infancy), it seems from these results that exposure through the skin is a strong candidate for contributing to the observed effects on development of peanut allergy.

Thus, if exposure to food proteins via the skin in early life is a probable route of sensitisation, and if (as has been observed from the rodent studies) early high dose oral exposure tends to induce tolerance to food proteins, then it might be the case that early dietary exposure of infants to potentially allergenic foods, particularly if this is in advance of exposure by another route (primarily skin), might be expected to encourage the development of tolerance and reduce the risks of sensitisation. This novel hypothesis has emerged from the above Agency funded research and from epidemiological observations by Du Toit et al. (2008) that the prevalence of peanut allergy among Jewish children in Israel who received early exposure to a weaning food rich in peanut protein was low, whereas prevalence of peanut allergy among Jewish children of the same age in the UK, where peanut is typically not introduced until an average of 32 months (Hourihane et al., 2007), is much higher.

This novel hypothesis is currently being tested via two recently commissioned studies to which the Agency is contributing; the LEAP study (Learning Early About Peanut Allergy) and the EAT study (Enquiring About Tolerance). The first of these is a randomised clinical intervention trial of the effects of early introduction of peanut into the infant diet for allergy prevention, in infants at high risk of developing peanut allergy, and during which blood samples are being taken to study the immunological acquisition of tolerance to peanut. The second is a randomised clinical trial of the early sequential introduction of 6 allergenic foods into the diet of infants drawn from the general population, alongside continued breastfeeding, on the prevention of food allergy and other health outcomes. If successful, the collective outputs from these major studies should provide more definitive information about whether early introduction of allergenic foods could be an effective strategy for the prevention of food allergy, and inform future UK policy in this area. Additionally, the Agency currently has an interest in exploring the relationships between skin barrier function, filaggrin loss of function mutations and the development of sensitisation and allergy to foods.

4. Concluding remarks

The focus of the Agency's Food Allergy and Intolerance Research Programme has been guided by the need to address important policy issues, and to provide sound and informed guidance to consumers, enforcement officers and the food industry. Nevertheless, in tackling specific policy needs it is clear that the Agency's investment in research has also contributed significantly to the scientific landscape and our understanding of the factors that impact on the acquisition of sensitisation to dietary proteins and the development of food allergy. Thus, as summarised here, the research commissioned by the Agency has, among other achievements, provided a much clearer picture of the prevalence of food allergy in the UK, an appreciation that food allergy may develop following the introduction of new foods into the national diet, important contributions to our understanding of the roles played by T lymphocytes and antibody in sensitisation and food allergy, and some intriguing indications that topical (skin) exposure to dietary proteins can result in the acquisition of sensitisation and allergy to foods. Current projects are seeking to further extend scientific knowledge and inform policy and advice in some of these areas, particularly with regard to improving our understanding of how the early life environment influences the development of sensitisation to food, which will inform future preventative strategies and risk characterisation.

Conflict of interest

None.

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