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**The Role of Precautionary Labelling for Food
Allergens and the Care of Children with Food Allergies**

A thesis submitted for the degree of Doctor of
Philosophy

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I dedicate this thesis to my father: Vincenzo Zurzolo and my mother: Felicia Zurzolo nee Bruzzaniti and to my children: Felicia, Isabella, Vincenzo and Giovanna Zurzolo. May this be a testament to you that nothing is impossible. (Yes, daddy did it.)

Finally I dedicate it to my brothers: Vincenzo, Guido and Francesco Zurzolo. All my most sincere gratitude for your support, love, and encouragement in the past, present and future.

Publications, Presentations and Scholarships during my Candidature

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Local & international presentations

Delivered a PowerPoint presentation on the 8th of April 2013 entitled, "The state of play of precautionary labelling in Australia" to the Department of Allergy at the Royal Children's Hospital, Melbourne.

Delivered an oral presentation on the 17th of June 2013 to the Gastro and Food Allergy group meeting at The Murdoch Childrens Research Institute.

Delivered an oral presentation on the 24th of July 2013 to the European Academy of Allergy and Clinical Immunology - World Allergy Organization (EAACI-WAO) at the World Allergy & Asthma Congress in Milan, Italy. The results of these studies were also used by Professor Katie Allen in her presentation to the EAACI-WAO World Allergy & Asthma Congress in Milan, Italy, during the conference (June 21-26 2013) as

well as by the Scientific Conference Affairs Committee working group and the international recommendations for precautionary labelling.

Delivered an oral presentation on the 9th of October 2013 to The Murdoch Childrens Research Institute and The Royal Children's Hospital titled "The concept of thresholds: do safe doses exist for food-allergic patients"?

Scholarships/Awards

I received a Victoria University Postgraduate Diversity scholarship to undertake my PhD studies. I was also awarded a top-up scholarship from the Murdoch Childrens Research Institute. I received a Secomb conference travel award from Victoria University to present my work at the EAACI-WAO World Allergy & Asthma Congress in Milan, Italy. In addition I also applied for and received a \$1,500 travel grant from the Murdoch Childrens Research Institute to present my work at the above-mentioned conference.

Further to this I received an outstanding achievement award from the Faculty of Biomedical and Health Sciences at Victoria University for Outstanding 3rd year research student.

Contents

Publications , Presentations and Scholarships during my Candidature.....	3
List of Tables and Figures	8
List of Abbreviations and Acronyms.....	9
Summary Abstract.....	11
General Declaration	17
Acknowledgements.....	19
Chapter 1: Introduction.....	21
Chapter 2: Literature review	23
2.1 IgE and non-IgE mediated food allergy.	23
2.2 How common is food allergy?.....	23
2.3 Is food allergy on the rise?	24
2.4 Food allergy and the atopic march.....	25
2.5 How is food allergy diagnosed?	26
2.6 How is food allergy managed?	27
2.7 How common are adverse events in those with food allergy?.....	29
2.8 What are the main causes of a serious adverse event in food allergy?.....	30
2.9 How do industry and regulators deal with helping to keep foods safe?	33
Chapter 3: What is the evidence that precautionary labelling is useful?	41
3.1 How common are precautionary statements?	42
3.2 How often are people reading food labels?.....	44
3.3 Testing and analysis of food products for cross contamination	46
3.4 Consumer attitudes and behaviour towards precautionary labelling	48
3.5 Voluntary Incidental Trace Allergen Labelling (VITAL) TM	51
3.6: Oral food challenges and the development of thresholds for the allergic consumer .	56
3.7 The state of play of precautionary labelling internationally	57
Aims.....	63
Hypothesis.....	65
Chapter 4: General materials and methods.....	66
4.1 Precautionary allergen labelling following new labelling practices in Australia.....	66

4.2 Consumer perceptions of precautionary labelling in families with food allergy and anaphylaxis in Australia.....	66
4.3 Foods with precautionary allergen labelling in Australia rarely contain detectable allergen.....	67
4.4 Hidden allergens in foods and implications for labelling and clinical care of food allergic patients.....	69
4.5 Peanut Allergen Threshold Study (PATS): validation of eliciting doses using a novel single-dose challenge protocol	69
Chapter 5: Precautionary allergen labelling following new labelling practice in Australia	71
Chapter 6: Perceptions of precautionary labelling among parents of children with food allergy and anaphylaxis.....	74
Chapter 7: Foods with precautionary allergen labelling in Australia rarely contain detectable allergen.....	82
Chapter 8: Hidden allergens in foods and implications for labelling and clinical care of food allergic patients.....	88
Chapter 9: Peanut Allergen Threshold Study (PATS): validation of eliciting doses using a novel single-dose challenge protocol	96
Chapter 10: Discussion, conclusion and future research direction	109
Chapter 11: References.....	117
Appendix 1: Consumer perceptions of precautionary labelling in families with food allergy and anaphylaxis in Australia questionnaire	122

List of Tables and Figures

Table 1: Advisory statements	35
Figure 1: Undeclared allergens	30
Table 2: The current precautionary statements in use	39
Table 3: VITAL1.0 action levels	50
Table 4: VITAL 2.0 reference dose	51
Figure 2: VITAL 2.0 decision tree	52
Table 5: International comparison of mandatory declarations on processed foods	58
Table 6: International comparison of voluntary declarations on processed foods	59

List of Abbreviations and Acronyms

AD	Atopic Dermatitis
ASCIA	The Australasian Society of Clinical Immunology and Allergy
Arah 1, 2, 3	Arachishypogaea (major peanut allergen)
AR	AllergicRhinoconjunctivitis
CHI 2	Pearson Chi-Squared tests
CI	Confidence Intervals
DBPCFC	Double-Blind Placebo-Controlled Food Challenges
ED	Eliciting doses
ED10	Eliciting doses that cause objective reactions in 10% of the population
ED05	Eliciting doses that cause objective reactions in 5% of the population
ELISA	Enzyme-Linked Immuno Sorbent Assay
FARRP	Food Allergy Research & Resource Program
FAQL	Food Allergy related Quality of Life
FLG	Filaggrin
FSANZ	Food Safety Australia New Zealand
GMP	Good Manufacturing Practice
HREC	Human Research Ethics Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G

kUA/L	Kilograms Units of Activity PerLitre
LOAEL	Lowest Observed Adverse Effect Level
NIAID	National Institute of Allergy and Infectious Disease
NOAEL	No Observed Adverse Effect Level
MCRI	Murdoch Childrens Research Institute
µG PER G	Micrograms Per Gram
OR	Odds Ratio
OFC	Oral Food Challenge
PPM	Parts Per Million
SCIT	Subcutaneous Immune Therapy
SLIT	Sublingual Immunotherapy
Stata	Statistics and Data
SPT	Skin Prick Test
T-CELLS	T Helper Cells
TH1	T Helper Type 1
TH2	T Helper Type 2
VITAL™	Voluntary Incidental Trace Allergen Labelling

Summary Abstract

There is no current cure for food allergy; therefore consumers with food allergy rely on accurate and detailed information on food labels in order to prevent an adverse reaction. Manufacturers cannot guarantee that food products are free from allergens as cross contamination can occur in several situations including but not limited to raw materials, the actual premises, storage and distribution, manufacturing processes and cleaning procedures. In order to alert the allergic consumer to the possible presence of trace allergens, manufacturers have voluntarily added precautionary labelling to processed foods. There are several variations to these statements, for example: “may contain traces of”, “may be present “and “made on the same production line”. The main purpose of this thesis is to understand the role of precautionary labelling in the care of children with food allergies.

The thesis focuses on two key areas of research. The first explores current practices with regard to precautionary labelling and the impact of these practices on food allergic consumers. This involved examining the prevalence of precautionary labelling in Australian supermarkets, perceptions and behaviours regarding precautionary labelling for food allergic consumers, and the level of allergen contained in foods with precautionary labelling. The second aimed to provide an evidence base to inform the development of new precautionary labelling practices which would be more useful for food allergic consumers. This involved a literature review and the development of protocol for a study to inform risk assessments for precautionary labelling for peanut allergic consumers.

European and US studies have shown that the use of precautionary labelling on packaged goods within a supermarket setting is very high. In turn this suggests consumers are exposing themselves to the possible risk of an adverse reaction by not adhering to these statements. Furthermore some consumers believe that these statements only protect the manufacturer from litigation.

My first study investigated the prevalence of precautionary labelling within Australia for peanuts, tree nuts, egg, milk, sesame, crustaceans, fish, wheat and soy and to investigate the uptake of the Voluntary Incidental Trace Allergen Labelling (VITAL) by manufacturers. (The VITAL process is funded the Australian Manufacturing industry and has been developed to replace all other forms of precautionary labelling. It incorporates a new precautionary statement: “may be present”. The process encourages manufacturers to undergo a more detailed assessment of their food products prior to labelling a food product with a precautionary statement.) In total, 1355 products were obtained from the supermarket setting and were investigated. Overall, 882 products (65%) had a precautionary statement for one or more allergens noted above. The most common allergens listed on precautionary statements were tree nuts (36.2%) and peanuts (34.1%), followed by sesame (27.5%) and egg (22.6%). Of those that had precautionary statements, “may contain traces of...” was the most common type of precautionary label used on 392 products (29.0%). This was followed by “may be present” on 172 products (12.7%). Although the uptake of the VITAL form of labelling: “may be present” was low in comparison to other precautionary statements, there has been an increase since 2009 when compared to a similar supermarket survey that was undertaken in Australia.

My second study investigated consumer behaviour and perceptions regarding precautionary labelling in those with and without a history of anaphylaxis. A questionnaire-based study of a consecutive series of 497 parents of children attending the Department of Allergy at the Royal Children's Hospital Melbourne was undertaken. Avoidance of foods with precautionary labels differed depending on the wording of the precautionary statement, with 65% of participants ignoring the statement "made in the same factory" compared with 22% for "may be present". There was no evidence of a difference in participants' behaviour or perceptions depending on whether or not the child had a history of anaphylaxis. Many statements are now being disregarded by a sizeable proportion of allergic consumers, including those caring for children with a history of anaphylaxis.

My third study investigated the level of cross contamination for peanut, hazelnut, milk, egg, soy and lupin in processed foods with precautionary statements by visiting three different Australian supermarkets in order to assess the risks taken by allergic consumers choosing to ignore precautionary labelling in the Australian setting. Five categories with a high prevalence of precautionary labelling were investigated, namely chocolates, breakfast cereals, muesli bars, savoury biscuits, and sweet biscuits (cookies). In total, 128 samples were assessed for allergen content analysis by Enzyme-Linked Immuno Sorbent Assay (ELISA) for peanut, hazelnut, milk, egg, soy and lupin protein. Of the 128 samples, only nine (7.0%) with precautionary labelling had detectable levels of peanut with concentrations ranging from >2.5ppm to <50ppm for

whole peanut, or >0.63ppm to <12.5ppm for peanut protein. Of all other samples that had precautionary labelling, none were found to have any detectable level of those allergens. In addition, of the food products that did contain detectable traces of peanut, none have been through the VITAL process.

My fourth study involved a detailed examination of the current literature regarding:

- 1) Precautionary labelling
- 2) Consumer behaviour and attitudes regarding this type of labelling
- 3) Risk to the consumer and the analytical results of products that bear advisory labelling
- 4) The current debate regarding whether a tolerable level of risk can be obtained in food allergy
- 5) The newly introduced Voluntary Incidental Trace Allergen Labelling (VITAL) system in Australia.

The study involved a comprehensive review of the literature and showed that within Europe and the US, precautionary labelling remains high; allergic consumers are not avoiding products that bear these labels and analytical results of products that bear advisory labelling contain minimal amounts of allergen which may not necessarily cause severe allergic reaction. The research suggests that a large collaborative study such as a one shot clinical trial is required to help provide further information about the ability of allergic individuals to tolerate a predefined low dose of allergen.

My fifth and final study investigated the validity of eliciting doses of peanut using a novel single dose protocol which may assist in the development of an objective risk assessment for peanut allergic consumers. The paper outlined the importance of eliciting dose (ED) for a peanut allergic reaction as it had been estimated for 5% of the allergic population. This is referred to as ED05 and has been calculated and modelled as 1.5 mg of peanut protein. This estimated ED05 was derived from multi dose oral food challenges (OFCs) that use graded, incremental doses administered at fixed time intervals, therefore the single dose to which the child reacts cannot be ascertained. The current study is a multi-centre study involving three teaching centres: University Hospital UCC Cork; Royal Children's Hospital Melbourne, Australia; and General Hospital, Food Allergies Centre, Massachusetts, U.S.A. A total of 375 participants were recruited during their follow-up appointments in the Department of Allergy in each respective centre. This paper aimed to assess the precision of the predicted ED05 using a single dose (6mg peanut = 1.5mg of peanut protein) in the form of a cookie. Validated Food Allergy related Quality of Life Questionnaires (FAQLQ) are available for all age groups and will be self-administered prior to the OFC and 1 month after the challenge. By using them we aimed to assess whether the impact of a positive "routine" diagnostic OFC can be as beneficial as a negative OFC. The study suggested that the single dose OFC, based upon the statistical dose-distribution analysis of past challenge trials, promises an efficient approach to identifying the most highly sensitive patients within any given food-allergic population.

In conclusion, this thesis shows that the prevalence of precautionary labelling is high and that food allergic consumers including those with children who have a history of

anaphylaxis are commonly ignoring precautionary statements on food products. Also those foods that do contain a precautionary statement infrequently contain any detectable allergen and that population based threshold appears to be a more effective risk assessment tool in the care of the allergic patient.

General Declaration

I, Giovanni Zurzolo, declare that the PhD thesis entitled “**The Role of Precautionary Labelling for Food Allergens and the Care of Children with Food Allergies**” submitted for the degree of **Doctor of Philosophy** is no more than 100,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work.



Signature

Date 2/12/14

PART A:
DETAILS OF INCLUDED PAPERS: THESIS BY PUBLICATION

Please list details of each Paper included in the thesis submission. Copies of published Papers and submitted and/or final draft Paper manuscripts should also be included in the thesis submission

Item/ Chapter No.	Paper Title	Publication Status (e.g. published, accepted for publication, to be revised and resubmitted, currently under review, unsubmitted but proposed to be submitted)	Publication Title and Details (e.g. date published, impact factor etc.)
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6	Perceptions of Precautionary Labelling among Parents of Children with Food Allergy and Anaphylaxis	Published	Published in June 2013 in <i>The Medical Journal of Australia</i> . I.F. 3.32
7	Foods with Precautionary Allergen Labelling in Australia Rarely Contain Detectable Allergen	Published	Published in May 2013 in <i>Journal of Allergy and Clinical Immunology: In Practice</i> . I.F. N/A
8	Hidden Allergens in Foods and Implications for Labelling and Clinical Care of Food Allergic Patients	Published	Published in May 2012 in <i>Current Allergy and Asthma Reports</i> . I.F. 2.5
9	Peanut Allergen Threshold Study (PATS): Validation of Eliciting Doses using a Novel Single-dose Challenge Protocol	Published	September 17 th 2013 to <i>Allergy, Asthma & Clinical Immunology</i> . I.F 3.03

Declaration by Giovanni Zurzolo

Signature: Giovanni Zurzolo

Date: 2/12/14

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Chapter 1: Introduction

It is currently estimated that one in ten children has a food allergy; the actual cause is uncertain at this stage but the prevalence may continue to rise. The management of food allergy basically involves abstinence from any food product that may contain an allergen to which a child is allergic and ongoing management including regular reviews to ensure the allergic plan is effective and to assess for tolerance development when appropriate. This includes consideration of the reintroduction of the allergen later in the child's life to see if that allergy has resolved. Processed foods are often used by parents of young children because of their accessibility and ease-of-use. Use of processed foods is more complicated for parents of children with food allergy because of concerns regarding trace contamination of allergens.

There are current regulations that deal with added ingredients in food products (including food allergens that are known to cause reactions in allergic children). The process is well governed and has been successful in alerting the consumer to the presence of added allergens and is referred to as mandatory labelling. However, modern manufacturing techniques cannot guarantee that a food product may be free from cross contamination from certain allergens due to processing, the use of shared equipment or exposure to other allergens through processing.

Therefore the manufacturing industry has incorporated the use of precautionary food labelling on many processed foods. The aim of precautionary labelling is to alert the consumer to the possible presence of certain allergens from cross contamination; the food ingredient has not been intentionally added to the product. An allergen that has been added during the manufacturing process requires a mandatory statement to that

effect. The types of statements that are used in precautionary labelling vary from “may contain traces of xxx (allergen)” to “made in the same premises as xxx (allergen)”. There is an abundance of these statements and there is no current regulation which controls their use. Due to the lack of regulations regarding precautionary labelling, it is uncertain whether or not there is any scientific process that validates the use of precautionary labelling on processed foods.

There is a current gap in the literature regarding the prevalence of precautionary food labels within the dominant supermarket companies in Australia and the behaviours and attitudes of parents with children who have food allergies. Also there is no information in Australia regarding the risk undertaken by parents should they choose to ignore precautionary labelling or whether products that contain precautionary labelling contain detectable levels of allergen. This thesis will address these gaps in the literature and provide evidence to inform precautionary labelling practices in Australia and internationally.

Chapter 2: Literature review

2.1 IgE and non-IgE mediated food allergy.

Acute allergy to food is mediated by immunoglobulin E (IgE) antibodies (1) which regulate systemic release of histamine from mast cells (2). Evidence exists of non-IgE mediated food allergies or delayed food allergies which may be mediated by IgG amongst other mechanisms (1). However these types of food allergy are poorly defined and rarely result in anaphylaxis.

2.2 How common is food allergy?

In Australia the most common types of food that children are sensitised to are peanut: 8.9% (95% CI, 7.9-10.0), egg: 16.5% (95% CI, 15.1-17.9), cow's milk: 5.6% (95% CI, 3.2-8.0) and sesame seed: 2.5% (95% CI, 2.0-3.1), with shellfish being rare in children. Adults are less often allergic to egg and milk (since most children grow out of these allergies) but more often to shellfish (3, 4).

An increase in prevalence of food allergy has been reported in developed countries as Sicherer 2010 et al. (2001) demonstrated in their study where they sought to determine the US's prevalence of self-reported peanut, tree nut, and sesame allergy in 2008 and compare results with similar surveys conducted in 1997 and 2002. The authors' results show that the population prevalence of childhood tree nut allergy increased significantly across the survey waves (1.1% in 2008, 0.5% in 2002 and 0.2% in 1997) (5).

2.3 Is food allergy on the rise?

The prevalence of food allergy has been studied in the general population (6). Sicherer et al. contacted 4855 participants through a random sampling of telephone numbers, with a response rate of 53%. The researchers reported an increase in self-reported peanut allergy from 0.6% to 1.2% in children from 1997 to 2002. Although this increase was significant in children, it was not statistically different in adults (6). In Great Britain the perceived prevalence of peanut allergy has been suggested to be approximately 0.5% in the adult population and 0.6% in children (n=124) (7). In Australia, Osborne et al. (2011) sampled a birth cohort of approximately 2848 infants (73% participation rate) from the population at 12 months of age. The authors' results revealed that more than 10% had food allergy to one of the common allergenic foods during infancy with peanut allergy at 3.0% (95% CI, 2.4-3.8); raw egg allergy at 8.9% (95% CI, 7.8-10.0); and sesame allergy at 0.8% (95% CI, 0.5-1.1). The diagnosis of food allergy was made using the gold standard: the oral food challenge, in a large unselected population. The strength of the study included the high participation rate and the high attendance rate at the food challenge clinic (84%) which would minimise the effect of selection bias. Also researchers performing the challenges were blind to both the SPT wheal size and the history of ingestion reaction (4). The study by Osborne et al. is unique because accurate or current prevalence data, particularly in infants and children younger than 3 years old, has not been available; previous estimates were based on parent or self-reported questionnaires or surveys. There have been few studies that confirm the prevalence of food allergy through the gold standard of the oral food challenge; however, even the few that have used the gold standard for confirmation of food allergy have been limited due to their poor participation rate (8).

2.4 Food allergy and the atopic march

The term atopic march refers to the natural history of allergic disease which begins with atopic dermatitis (AD), and progresses to food allergy, allergic rhinitis, and asthma (9). The atopic march affects approximately 20% of the population in developed countries (10). AD is a common chronic pruritic skin disease seen in infants and children. A search of the literature reveals that there may be a positive association between food allergy and AD (11-16). Of the literature that is available, researchers have investigated the association of peanut, cow's milk, and egg allergies with AD. However there is debate about which comes first: AD then food allergy or the reverse (17). Several authors have been able to demonstrate an association between food sensitisation/allergy and AD (18, 19). Eller et al. (2009) reported that 43% of their cohort that had sensitisation to food also had AD (n=562). The researchers also found that children who had sensitisation over a greater period of time had the more rigorous form of AD (12).

Kijima et al. (2013) showed that food allergy is a burden on society because of the development of other allergic disease. It can lower the quality of life and work productivity of affected patients and their families. The authors interviewed 3321 participants and asked questions regarding family history of atopic disease such as Atopic Dermatitis (AD), Bronchial Asthma (BA), Allergic Rhinitis (AR) and also of Food Allergy (FA). Histories of AD, BA, AR, and FA were based on a doctor's diagnosis at any time during the participant's life from birth to the present day. The investigators showed that FA significantly raised the risk of allergic disease comorbidity (AD, BA, and AR), especially AD, and critically increased the number of diseases (20).

Penard-Morand et al. (2005) and Ostblom et al. (2008) have shown that if food allergy develops at a young age, this early onset of IgE mediated allergy increased the risk of AD, BA, and AR at 8-11 years of age (21, 22).

We are currently facing rising rates of food allergy. This may potentially add to the burden on society through the development of other allergic diseases if food allergy is found to be part of the atopic march (23).

2.5 How is food allergy diagnosed?

An allergist will consider many variables when diagnosing a patient with food allergy, these include the patient's history, skin prick testing and the measurement of food-specific immunoglobulin E antibodies, however, none of these parameters can accurately predict tolerance. The gold standard for diagnosis of IgE food allergies is the Double-Blind, Placebo-Controlled Food Challenge (DBPCFC) because specific IgE, skin prick tests and history often do not correlate well with clinical reactivity (1).

Allen et al. (2006) explained that Challenge protocols are based on increasing oral doses of food allergen, beginning at a very low dose. The doses are administered at predetermined time intervals until the first symptoms occur. Open label or Oral Food Challenges (OFC) is usually sufficient in clinical practice, as long as symptoms can be objectively assessed. DBPCFC are used for patients with subjective symptoms or in the research setting. Confirmed diagnosis is essential as this will distinguish between perceived food allergies and true food allergies (8).

Elimination diets are recommended for sufferers of food allergy; however unnecessarily restrictive elimination diets should be avoided especially in early childhood, since they

are associated with the risk of malnutrition and increased emotional stress (24). As previously mentioned there are different methods used for the diagnosis of food allergy, but may not be as accurate as the OFC, these are positive history of food allergy in conjunction with a $>3\text{mm}$ SPT or blood test for a measurement of specific IgE antibodies to a specific protein within the range of 0.35 to 100 kUA/L (25). In addition there are new developments in component-resolved diagnostic (CRD). This method examines the natural purified or recombinant peanut proteins and the measurement of circulating IgE directed toward these specific protein components, Ara h 2 is the most important component in relation to peanut allergy (26).

However the OFC is resource-consuming and may be potentially dangerous. To reduce the need for an OFC there is currently debate about whether an SPT wheal size exceeds a cut-off point and whether that size can be used as a predictor for the diagnosis of food allergy without the need to perform an OFC (27).

2.6 How is food allergy managed?

Currently there is no cure for food allergy; the mainstay of management is strict avoidance of the offending food until the individual has grown out of their food allergy. However some children may never grow out of their allergy. This is particularly true for children with peanut allergy. The key success to strict avoidance is to have clear and concise information on food products so that the allergic consumer feels reassured that the product is safe for consumption. Food labels should be informative, reliable and help parents with children who have food allergy in their management of food allergy. Allergen avoidance is the only safe method in keeping a child that has food allergy safe from a possible life-threatening reaction such as anaphylaxis. Living with food allergy

might seriously affect the quality of life of both patients and children with food allergy. Food allergic individuals are often afraid of allergic reactions from accidental exposure and are continuously faced with dietary and social restrictions (28).

Cummings et al. (2010) investigated how the management of children with nut allergy influenced theirs and their mother's quality of life. The authors used a cross-sectional questionnaire measuring quality of life (QoL), anxiety and stress in nut allergic children aged between 6 to 16 years and their mothers (41 children and 41 mothers). Participants were recruited from a university paediatric hospital and the diagnosis of nut allergy was made by paediatric allergists (29).

The results of this investigation showed that food allergy significantly impacts on the quality of life of children with food allergy and their carers, as it showed significantly high levels of stress and anxiety in the study population. It was of interest that girls reported higher levels of stress and anxiety than boys. Also, participants who chose to ignore precautionary labelling reported lower stress and anxiety levels compared to those who chose not to ignore these statements.

A limitation of the study is the low participation rate and that the disease-specific quality of life questionnaire was not used as a measurement. Therefore the authors chose to use validated generic QoL questionnaires, designed to measure QoL in the general population. The results may have been different if the authors were able to use recently developed validated quality of life questionnaires specifically for food allergy which are now available (30).

2.7 How common are adverse events in those with food allergy?

The most severe type of objective reaction to food is anaphylaxis. Anaphylaxis is defined as a severe, life-threatening, generalised hypersensitivity reaction involving several systems including the respiratory tract and the cardiovascular system. Typical manifestations include stridor, breathing difficulties or wheezing and lowered blood pressure (31). Anaphylaxis is responsible for over 30,000 hospital emergency admissions in the United States alone and it has been estimated that 150-200 deaths each year are a direct result of food induced anaphylaxis. In Australia, Brown et al. (2013) investigated the rates of anaphylaxis by examining eight Australian emergency departments (ED) and recruiting patients from 2006-2009. The authors' results showed that during this time period, 433 patients were admitted to the ED due to anaphylaxis. The suspected cause of these admissions in 43% was food (32).

Peanuts, tree nuts, fish and shellfish account for the most severe types of reactions (33). Sampson et al. (2006) observed a high degree of risk-taking amongst adolescents. The researchers recruited 174 participants aged between 16 and 21 years old via internet-based questionnaires. The questionnaires were designed to gain an insight into the risk-taking behaviours of participants with food allergy. Of those who participated, 86% had been prescribed self-injectable adrenaline and 71% had had a history of anaphylaxis due to risk-taking behaviours. Regarding risk taking behaviours, 42% of participants reported that they ignored precautionary statements and consumed foods with these statements irrespective of their allergy. It is possible to postulate that this type of behaviour by adolescents of ignoring precautionary labelling may have contributed to the high rate of adverse reaction as seen in this study. However the researchers relied on self-reported anaphylaxis as the diagnosis for an adverse reaction. Medical diagnosis of

anaphylaxis with confirmed objective symptoms may have seen the results of adverse reactions far less than reported in this study (34).

2.8 What are the main causes of a serious adverse event in food allergy?

Accidental food-induced anaphylactic reactions

Sampson et al. (2003) estimated that 30 000 food-induced anaphylactic reactions occur in the United States each year which result in 2000 hospitalisations. Food was estimated to account for more than one third of the anaphylactic reactions treated in emergency departments with the majority being due to accidental ingestion of peanut, tree nuts or fish (33). In Australia, Braganza et al. (2006) examined the incidence of anaphylaxis presentations in the inpatients under 16 years old over a three year period at an emergency department. In total, 583 patients were investigated. Of these, 526 were classified as either having generalised allergic reactions, which gave a population prevalence of 7.4 cases per 1000 children, or 57 with anaphylaxis which gave a population prevalence of 0.8 cases per 1000 children. The reported cause for 40% of these events in the generalised allergic reactions group and 68% in the anaphylaxis group was food, the most common being eggs, dairy and peanut (35).

Hoffer et al. 2011 investigated the events of children admitted to a Medical Centre in Israel over a 12 year period by reviewing medical charts. 92 children with anaphylaxis aged between 14 days to 18 years old were hospitalised during this period. More than half of these children had a history of atopic disease and 22% had a past positive SPT to food allergens. Interestingly 12% of children had a history of food allergy which was not proven by allergy testing. The authors' results showed that in 56% of children

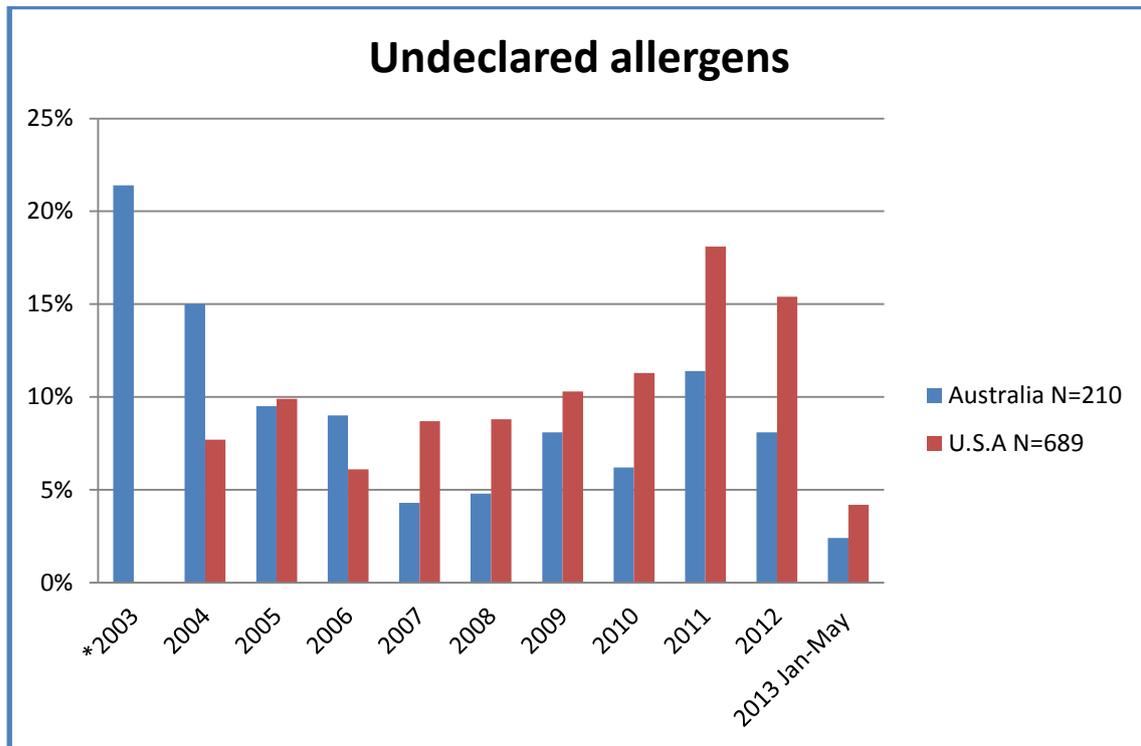
admitted to the medical centre for treatment, the event occurred at home and that the main cause was foods (43%) that derived from milk and nuts (36). The authors provided no information on the exact process of how these events occurred, for instance did anaphylaxis occur in these participants due to ingestion of processed foods? Were the participants ignoring precautionary statements?

Food recalls in Australia, New Zealand and the USA

Undeclared allergens or inappropriate labelling may result in accidental ingestion by an allergic consumer, which may lead to life threatening reactions such as anaphylaxis. Food Standards Australia New Zealand (FSANZ) is an independent statutory agency established by the Food Standards Australia New Zealand Act 1991. FSANZ develops food standards to cover the food industry in Australia and New Zealand; they are also responsible for the labelling of both packaged and unpackaged food, including specific mandatory warnings or advisory labels. In addition, they carefully monitor food recalls within the food manufacturing industry. In a ten year period FSANZ has coordinated the recall of more than 200 processed food products that had undeclared allergens (37) (Figure 1).

Figure 1: Undeclared allergens - the number of recalls in Australia and the USA from 2003 to 2013

** No data was available in 2003 for the USA.*



This data was sourced from the Food Standards Australia New Zealand website (37) and the US Food and Drug Administration (38).

Since the establishment of legislation in 2003 in Australia and New Zealand which resulted in the introduction of mandatory labelling, the recalls have remained steady. In the US, the Food and Drug Administration (FDA) operate in a similar fashion. Since 2004 the FDA have documented 689 food recalls due to undeclared allergens (38). However the rate of food recalls due to undeclared allergens is increasing since the establishment of legislation in 2003. This is contrary to what we see in Australia (Figure 1), though it is unclear whether the recalls were due to manufacturers, wholesalers, retailers, government agencies, consumers or a combination of all of the above. In addition it would be plausible to suggest that recalls initiated by food allergic consumers

would result in an increase in reported recall cases due to those consumers being anxious about a possible reaction (39, 40).

2.9 How do industry and regulators deal with helping to keep foods safe?

As described above, since there is no established cure for food allergy, the mainstay of management is complete avoidance of all foods that contain the causative allergen. In 2003, food labelling legislation was introduced in Australia and New Zealand (FSANZ), followed by similar legislation introduced by the European Commission and the US Congress in 2003-2004 (41-43). Under standard 1.2.3 of the Food Standards Australia New Zealand Act 1991 (mandatory warning and advisory statements and declarations), food labels are required to provide different levels of advice for consumers depending on the food and its ingredients. This advice is as follows:

Mandatory warning statements – this is a specific labelling statement which must be provided in the exact words and format approved by FSANZ and its code. It must also have a 3mm minimum font size and in the case of small packages, 1.5 mm.

Currently the only foods which must contain warning statements are: Royal Jelly when presented as a food; any food containing Royal Jelly as an ingredient; Kava; infant formula products; infant foods; and formulated supplementary sports foods. When Royal Jelly is presented as a food or as an ingredient in a food, it is required to be labelled with the statement, “This product contains Royal Jelly which has been reported to cause severe allergic reactions and in rare cases, fatalities, especially in asthma and allergy sufferers”.

Powdered, concentrated and ready to drink infant formula products are required to be labelled with the statement, “Warning – follow instructions exactly. Prepare bottles and teats as directed. Do not dilute or add anything to this ‘ready to drink’ formula except on medical advice. Incorrect preparation can make your baby very ill”. This is followed by the statement, “Breast milk is best for baby. Before you decide to use this product, consult your doctor or health worker for advice”.

For products that contain Kava, the statement must read, “Use in moderation, may cause drowsiness” and for formulated supplementary sports foods, the label must read, “Not suitable for children under 15 years of age or pregnant women: should only be used under medical or dietetic supervision”. If a formulated supplementary sports food contains added phenylalanine the label must also read “Phenylketonurics: Contains Phenylalanine” (41).

Mandatory advisory statements

These are advisory statements on certain foods or when certain substances are present in foods. The language and format of these statements are not prescribed. The manufacturer can use their own language as long as it conveys the intended effect (this is therefore different to warning statements where the language and format in relation to font size is prescribed and cannot be changed). For example, bee pollen presented as a food or as an ingredient in a food, is required to be labelled with a statement to the effect of “this product contains bee pollen which can cause severe allergic reactions”. With evaporated milks, dried milks and equivalent products made from soy or cereals, where these foods contain no more than 2.5% of the finished product, a statement is

needed to the effect that the product is not suitable as a complete milk replacement for children under the age of five years (Table 1) , (41).

Mandatory declarations of certain substances in food – the code recognises that certain substances frequently cause severe systemic reactions resulting in significant morbidity or mortality as in the case of consumers who have food allergy. Certain food components must be declared on food labels (most usually included in the ingredients list). Currently, the presence of the following foods, ingredients, or their products must be declared: cereals containing gluten and their products, namely, wheat, rye, barley, oats and spelt and their hybridised strains; crustaceans and their products; eggs and egg products; fish and their products; peanuts and soybeans and their products; milk and milk products; tree nuts (including almonds, brazil nuts, cashews, chestnuts, hazelnuts, hickory nuts, macadamia nuts, pecans, pine nuts, pistachios and walnuts); sesame seeds and their products; and added sulphites in concentrations of 10 mg/kg or more. The code requires declaration of these substances on labels when they are present in a food as an ingredient, an ingredient of a compound ingredient, a food additive, a component of a food additive, a processing aid or a component of a processing aid irrespective of the degree of refinement or modification of the substance (41). These declarations are to alert the consumers affected by these substances that the food products contain substances that may cause adverse reactions. Including these substances in a statement of ingredients fulfils the declaration requirements.

Genetically modified (GM) food

GM foods, ingredients, additives, or processing aids that contain novel DNA or protein must be labelled with the words ‘genetically modified’. Labelling is also required when

genetic modification results in an altered characteristic in a food, e.g. soy beans with changed nutritional characteristics such as an increase in oleic acid content (41).

Food additives

All food additives must be labelled, however food additive names can be confusing. To help reduce this confusion, each food additive is given a short code number which is identified for the consumer on the FSANZ website (41).

Hormone additions

There are no hormones added to processed foods in Australia, however hormonal growth promotants (HGP) such as oestrogen, progesterone and testosterone or synthetic alternatives such as trenbolone, acetate and zeranol are used in about 40% of cattle to accelerate weight gain and have been used for the past 30 years in Australia. This practice ceased in 1960 for chicken, however antibiotics are still currently used. Foods derived from animals that have received HGP contain no labelling regarding these practices. The European Union (EU) has banned their use and will not import products from cattle given HGP (37).

Country of origin

All packaged and some unpackaged foods sold in Australia must be accompanied by information stating where the food comes from (the country of origin). Country of Origin Labelling has been extended to apply to unpackaged beef, sheep and chicken meat as of the 18th of July 2013 (37).

Table 1: Advisory statements

Food	Advisory statement
Bee pollen presented as a food, or a food containing bee pollen as an ingredient as defined in Standard 1.2.4	Statement to the effect that the product contains bee pollen which can cause severe allergic reactions.
Cereal-based beverages, where these foods contain no more than 2.5% m/m fat and less than 3% m/m protein, or less than 3% m/m protein only.	Statement to the effect that the product is not suitable as a complete milk replacement for children under the age of five years.
Evaporated and dried products made from cereals, where these foods contain no more than 2.5% m/m fat and less than 3% m/m protein, or less than 3% m/m protein only, as reconstituted according to directions for direct consumption.	Statement to the effect that the product is not suitable as a complete milk replacement for children under the age of five years.
Evaporated milks, dried milks and equivalent products made from soy or cereals, where these foods contain no more than 2.5% m/m fat as reconstituted according to directions for direct consumption.	Statement to the effect that the product is not suitable as a complete milk food for children under the age of two years.
Food containing aspartame or aspartame-acesulphame salt	Statement to the effect that the product contains phenylalanine
Food containing quinine	Statement to the effect that the product contains quinine
Food containing guarana or extracts of guarana	Statement to the effect that the product contains caffeine
Foods containing added phytosterols, phytostanols or their esters	Statements to the effect that – 1. when consuming this product, it should be consumed as part of a healthy diet; 2. this product may not be suitable for children under the age of five years and pregnant or lactating women; and 3. plant sterols do not provide additional benefits when consumed in excess of three grams per day.
Cola beverages containing added caffeine, or food containing a cola beverage containing added caffeine as an ingredient as defined in Standard 1.2.4.	Statement to the effect that the product contains caffeine
Milk, and beverages made from soy or cereals, where these foods contain no more than 2.5% m/m fat.	Statement to the effect that the product is not suitable as a complete milk food for children under the age of two years
Propolis presented as a food, or food containing propolis as an ingredient as defined in Standard 1.2.4	Statement to the effect that the product contains propolis which can cause severe allergic reactions
Unpasteurised egg products	Statement to the effect that the product is unpasteurised
Unpasteurised milk and unpasteurised liquid milk products	Statement to the effect that the product has not been pasteurised

This information was sourced from the Food Standards Australia New Zealand (FSANZ) website (37).

As mentioned above, these declarations are required by law to provide advice to consumers regarding the product ingredient list. The study by Simons et al. (2005) of 489 allergic participants demonstrated that consumers do not truly understand these statements as 16% of participants investigated reported that allergic reactions were attributed to misunderstanding label terms and 22% to misunderstanding terms such as spice and flavour (44).

However the study by Simons et al. (2005) examined children and young adults who may not have read information labels as carefully as a parent or caregiver. In addition, the study gained information only through questionnaires, an avenue which may have resulted in recall bias (44).

The authors suggested that clear and consistent labelling of food allergens combined with increased consumer education is necessary to improve consumer confidence and compliance and that this may reduce accidental exposures(44).

Weber et al. (2007) investigated 47 parents of children on cow's-milk-free diets to determine whether they were able to recognise different expressions of cow milk protein. The authors' results showed that less than 25% of those interviewed recognised casein, caseinate, lactalbumin and lactoglobulin as a cow's milk protein on food products (45). It is interesting to note that in Australia it is mandatory to use cow's milk and other readily recognised terms for the consumer rather than casein. A limitation of this study is the low number of participants recruited (N=47), but it is interesting to note that although participants received guidance on how to read food labels, they were still not able to correctly identify milk protein following this education.

During 2004, the Food Safety Australia New Zealand (FSANZ) conducted a survey of 1166 potential participants in both Australia and New Zealand who were identified by medical specialists as being at risk of adverse or allergic reaction. 510 participants responded (413 from Australia and 97 from NZ) with an overall response rate of 44% (46). The study focussed on a selection of substances listed in Standard 1.2.3 Mandatory Warning and Advisory Statements and Declarations. These were wheat (gluten-containing-cereals and their products); eggs and egg products; fish and fish products; milk and milk products; nuts and sesame seeds (including their products); peanuts and soybeans (including their products) and added sulphites. The study found that 42% of participants had a reaction after their first diagnosis of food allergy. The main reasons for this repeated reaction were accidental consumption (36%), contact with the substance of concern (21%), unlabelled or incorrectly labelled food (14%) and traces of substances in unexpected foods (6%).

In 2009 FSANZ repeated the study with a revised and shortened methodology. Similarly, 50% of participants had a reaction after their first diagnosis of food allergy and the main reason for the reaction was a result of accidental consumption of the ingredient (45%) which was due to misunderstanding food labels, unlabelled or incorrectly labelled food (5%) (47).

It is evident from the studies above that consumers do not understand mandatory statements. Added clarity and detail on ingredients lists is required. The FSANZ studies in 2003 and 2009 have helped to improve mandatory statements by their implementation of certain changes which include the use of consistent names (no conflicting names) for the same ingredients (Soy Sauce Extract, Soybean) and the use of plain English (Sodium Caseinate From Milk) in the place of scientific names

(Emulsifier, Soy Lecithin) and codes (153, Vegetable carbon) and the content of derivatives, such as emulsifiers so that all consumers can understand.

Chapter 3: What is the evidence that precautionary labelling is useful?

Despite the best efforts of manufacturers, hidden allergens can occur in foods via cross-contamination from the use of shared equipment or facilities, packaging errors or issues related to the supply chain. This has prompted manufacturers to introduce precautionary labelling. Because these statements are not mandatory, a variety of statements are currently used (Table 3), (48).

Table 2: The current precautionary statements in use

May contain	May contain traces of	Made on the same production line	Manufactured in a facility that also processes
Manufactured on a line that processes	Packaged in a facility that also packages products containing	Processed on equipment that makes products containing	Produced in a plant which manufactures products containing
Made on the same equipment	Made in the same factory	Made in the same premises	May be present

At the point of consumption, food products may have become cross-contaminated with residues of allergens due to shared farming facilities, harvesting equipment, storage facilities, shared transportation vehicles, shared processing facilities and shared processing equipment (49). This cross-contamination can leave a food allergic patient exposed to any of the symptoms that can occur in a food allergic reaction, from hives to life-threatening anaphylaxis.

Hefle et al. (2007) undertook a survey-based examination to try to determine if consumers with food allergy heeded precautionary labels. The authors recruited participants in 2003 (n=652) and 2006 (n=645). Parents of children with food allergy were presented with a list of precautionary statements and asked to indicate how often they purchase foods with those statements on their labels. The authors' results showed that there was a significant difference ($p < .002$) in the rate in which different labels were heeded between the observed years. In 2003, 85% of participants reported that they would “never” purchase a product with a precautionary statement compared with 75% in 2006 (50). However anecdotally there appears to be an increasing number of consumers with food allergy who are not heeding precautionary statements and are ingesting foods that contain these statements in their labels (K. Allen, personal communication, August 15, 2013). The participants from the above study were recruited from patients’ conferences; therefore it may be possible to suggest that these participants were very concerned individuals and would be more vigilant about avoidance diets.

3.1 How common are precautionary statements?

The prevalence of precautionary statements on packaged goods has been reported to be high in Australia, Europe and the US. Koplin et al (2010) assessed the prevalence of advisory labelling in several categories of processed foods within a large supermarket in Australia. The most common allergens that had precautionary labelling were tree nuts at 50%, peanut at 47% and egg at 23%. However this high prevalence was only investigated for the above allergens and the other mandatory allergens were not investigated (51).

The study by Pele et al. (2007) of 10 European countries investigated 300 biscuits and found that the overall prevalence of precautionary allergen labelling for peanuts, hazelnut or nuts was 50% respectively (52). A limitation of this study is that only peanuts and tree nuts were examined but no other common allergens.

The study by Ford et al. (2010) sampled products from multiple supermarkets in New York and New Jersey to examine the prevalence of precautionary statements among 401 samples of products that contained precautionary statements for egg, milk and peanut. The authors' results showed that the prevalence of precautionary allergen labelling for egg was 14.2%, milk: 14.7 and peanut: 27.5 % (53).

In contrast in Canada Vadas et al. (2003) examined the presence of peanut protein in chocolate bars produced in Europe and North America that did not list peanuts as an ingredient. Ninety-two chocolate bars, of which 32 were manufactured in North America and 60 were imported from Europe, were tested. None of the 32 North American chocolate products, including 19 with precautionary labeling, contained detectable peanut protein. However 30.8% of products from western Europe without precautionary labeling contained detectable levels of peanut protein and 62% of products from eastern Europe without precautionary labeling contained detectable peanut protein (54).

The largest study to date is by Pieretti et al. (2009) in the US in which trained surveyors performed a supermarket survey of 20, 241 products from 99 different supermarkets to investigate advisory labels. They were instructed to choose products randomly by as many manufacturers as possible to obtain a wide

representation. A total of 500 products per supermarket location were audited. Overall 17% of products contained precautionary statements with the highest use of precautionary labelling being for chocolate at 54%. The most common allergen listed in precautionary statements was tree nuts at 61% (55).

3.2 How often are people reading food labels?

Recently in the UK Barnett et al. (2011) examined the risk undertaken by peanut and generally nut allergic consumers when buying products for consumption. The behaviour and thinking aloud of 32 participants were recorded during their normal food shop and this was followed by an interview which was designed to gain participants' knowledge of food labelling. The results showed that participants used product brands or names as a source for their assessments. When this did not help them, other information was used such as ingredients lists. Participants would often choose brands and supermarkets that they considered reputable and the well-known brands were trusted more in relation to precautionary statements. In addition, participants felt that greater standardisation was needed and that statements such as "free from xxx (allergen)" would be far better than the current precautionary statements that are in use (56).

In Canada, Sheth et al. (2009) investigated 1,454 food-allergic individuals to determine the proportion of food-allergic individuals who attributed an accidental exposure to inappropriate labelling. Participants were recruited from a registry of individuals with confirmed diagnosis of peanut allergy. The authors' results showed that 47.0% (95% CI, 43.1%–50.9%) attributed the event to inappropriate labelling.

This high prevalence is troubling as this proportion of participants may have an increased risk of life-threatening reactions such as anaphylaxis. However, the authors gained information via questionnaires regarding accidental exposures due to specific food labelling issues and this method may have led to recall bias since the reported cases were not independently assessed for labels (57).

These studies collectively show that there is a need for additional education regarding precautionary labelling as the majority of food allergic consumers do not understand this type of labelling. Recently this was also seen in the study by Worth et al. (2013) in which the authors investigated the issues experienced by young adults aged from 15-25 years with anaphylaxis. A total of 1, 317 parents of young adults were identified as a target group from an anaphylaxis database which consisted of parents of children who had been prescribed an epinephrine auto-injector and were signed up to receive an anaphylaxis campaign newsletter . The prospective participants were contacted via email and asked to complete an online questionnaire. In total, 520 (39% response rate) completed the online questionnaire. A total of 56% of participants reported their main approach for managing their anaphylaxis to be taking note of food labelling, however 43% of participants desired more information on food labelling (58).

The above studies have investigated the prevalence of precautionary allergen labelling for peanut, tree nut, egg and milk only. No other study to date has investigated the proportion of products with any precautionary labelling in an Australian supermarket to any of the 9 most common allergens (peanuts, tree nuts, egg, milk, sesame, crustaceans, fish, wheat and soy). In addition, no study has yet formally

investigated the newly developed VITAL precautionary labelling system which has recently been developed by industry for food manufacturers.

3.3 Testing and analysis of food products for cross contamination

Cross contamination is a common cause of accidental exposure of food allergic patients to an allergen (49). This has been well-documented for milk (59, 60), peanut(61, 62), crustacean (63) and hazelnut (64). However the published reports, including those previously mentioned, typically involve only one or a few patients.

Recently Anibarro et al. (2007) investigated the prevalence of accidental exposure to egg and fish in a retrospective study. Over a five-year period, 530 food reactions were investigated. More than 22% of reactions were due to hidden allergens. Alarmingly, 32% of these were anaphylactic reactions. Fish was the major allergen noted as the most common hidden allergen at 35%, followed by egg at 22% (65).

A major element of a good manufacturing process is the testing of food products for trace contamination. Testing for food allergens is a valuable tool when used as part of a risk-based approach to allergen management. Test results can provide assurance and verification of critical controls within a comprehensive risk management program. The most commonly used analytical method for detecting the presence of food allergens is the Enzyme Linked Immuno Sorbent Assay (ELISA) technique. Unfortunately ELISA is not incorporated into all risk management programs, particularly not those for precautionary labelling, as the use of ELISA is up to the discretion of the manufacturer. The benefit of using these kits is that they are easy to use and are sensitive and specific

for food protein detection (66). The ELISA kits currently available have a low parts per million (ppm) reporting range (67).

However the ELISA kits do contain certain limitations. These are that:

- 1) The kits are unable to determine the effect of processing on the allergens
- 2) The effects of processing may interfere with critical steps of immunoassays
- 3) The food matrix may also cross-react with antibodies of the kits, resulting in false-positive results (66).

In addition Allergen tests using the Enzyme-Linked Immunosorbent Assays (ELISA) technique are not applicable for use in certain situations. Because the tests are based on an antibody reaction with the extracted allergenic protein, the protein in the sample must be close to its natural state and readily extractable. Although this is normally the case, in certain instances the test may not yield results totally indicative of the sample's potential to produce an allergic reaction in susceptible consumers. Some of these instances include (but are not limited to):

Hydrolysed proteins;

Proteolised proteins;

Fermented products and products microbially grown on allergenic substrates; and

Probiotic cultures and enzyme preps (68).

In Europe, Vadas et al. (2003) tested for the presence of peanut protein in 92 chocolate bars produced in Europe and North America. None of the products in North America (including 19 that had precautionary labelling for peanut) contained detectable peanut protein. In contrast, more than 30.8% of products from Europe without precautionary labelling contained detectable levels of peanut (54). This study showed that without a standardised process that is backed up by sound scientific evidence, there will continue

to be a lack of consistency amongst manufacturers regarding the ways in which precautionary statements are used.

For a further examination of the above topics please see the manuscripts entitled, “Hidden Allergens in Food and Implications for Labelling and Clinical Care of Food Allergic Patients” and “Foods with Precautionary Allergen Labelling in Australia Rarely Contain Detectable Allergen” in the results section of this thesis (chapters 8 and 7 respectively).

3.4 Consumer attitudes and behaviour towards precautionary labelling

Consumers with food allergy are often advised to avoid products with precautionary statements even though the exact risks are unknown (69). Research shows that cross-contamination is a common cause of accidental exposure of food allergic patients to an allergen (49). However there is evidence that threshold levels below which reactions are not provoked in allergic individuals do exist, suggesting that precautionary labelling may be unnecessary where any possible trace contamination is below these thresholds (70).

Precautionary food labelling is used by manufacturers to indicate the possible presence of trace allergens; however food labelling legislation does not address this issue. Barnett et al. (2011) investigated how peanut and nut allergic participants (aged from 16 and over) interpret precautionary labelling and how they use this information when purchasing food. The behaviours and attitudes of 32 peanut allergic participants were assessed during the participants' routine shopping. The

authors' results show that the majority of participants ignored precautionary labelling when making a decision to purchase a product. In addition, many participants ignored precautionary labelling because they had already bought and consumed products with this type of labelling (with no reaction) and felt that labels were untrustworthy (71). This small study provided interesting qualitative data but almost all of it was undertaken with adult consumers; no study to date has investigated the behaviours and attitudes of parents with children who have a history of anaphylaxis.

By comparison, a small study in the UK conducted interviews with people with a nut allergy, either by themselves or with a parent or partner who shopped for them on a regular basis. They investigated the study group's attitudes and behaviour regarding precautionary labelling. Nut allergy was defined by either self-diagnosed or doctor-diagnosed food allergy to a variety of nuts. The study found that the widespread usage of precautionary labelling resulted in consumers feeling restricted when shopping and that the label lacked credibility (72).

Furthermore, the study found that food allergic consumers were risk-taking; they took calculated risks when deciding which foods to eat. This study highlighted consumers' behaviour regarding precautionary labelling, however a limitation of the study is the very low participant rate of < 20 participants. Another limitation is the researchers' definition of food allergy (the parent report) as this may not give us the required information regarding the attitudes and behaviours of those with true food allergies.

In addition, food allergic consumers' attitudes and behaviours regarding precautionary labelling can often be influenced by expert advice as there is a known divergence of medical advice to patients regarding family adherence to advisory labels. Some services advise complete avoidance of all foods with advisory labels, whereas others support continued consumption of foods already eaten safely even if advisory labels are present, but advise against the consumption of labelled foods that have not been previously consumed (J. Hourihane, personal communication October 2, 2012). Other services advise patients that the labels are confusing, voluntary and not rationally applied and that therefore the only safe way to avoid allergen contamination is not to eat any manufactured goods (see below- Department of Allergy RCH).

Anecdotally, allergists vary their advice based on an informed judgement of who is at greatest risk for a severe adverse reaction. Those who are extremely sensitive are both more likely to be told to avoid food with precautionary labelling and also more likely to self-impose restrictions from fear of experiencing a severe accidental reaction from ingestion of even a trace amount, but to date no study has formally addressed this.

In the Department of Allergy at the Royal Children's Hospital, (RCH) Melbourne, Australia, the following passage is incorporated into the allergen avoidance patient information sheet.

“These statements are used by manufacturers to indicate that the product may be contaminated with peanut through processing and packaging. At present these statements are voluntary and there are no clear guidelines for companies regarding how and when to use them. The wording of the statements makes it very difficult to determine your level of risk and a product that does not contain the statement may be no safer than a product that does. The chances of having a significant allergic reaction through

contamination during processing are extremely unlikely. People with severe or anaphylactic reactions should use these products with caution. The only safe alternative is extremely limiting as it would be to not include any commercial food products in your child's diet. For children with severe allergic reactions, companies can be contacted directly to explore food processing, packaging and cleaning procedures".

There is currently a gap in the literature regarding food allergic consumers' attitudes and behaviours to precautionary labelling in the Australian setting. This data would prove to be useful to help validate the information that parents receive from the RCH allergen avoidance patient information sheet.

For a further examination of these topics please see the manuscript entitled, "Hidden Allergens in Food and Implications for Labelling and Clinical Care of Food Allergic Patients" in the results section of this thesis (chapter 8).

3.5 Voluntary Incidental Trace Allergen Labelling (VITAL)TM

In 2006 the UK Food Standards Agency reported to manufacturers that advisory labelling should only be used following a thorough risk assessment that will have found that a real risk of allergen cross-contamination still exists (73). Voluntary Incidental Trace Allergen Labelling (VITAL) is currently the most scientific system of action levels to deal with possible cross-contamination.

The VITAL process has been developed to replace all other forms of precautionary labelling and incorporates a new precautionary statement: "may be present". The process encourages manufacturers to undergo a more detailed assessment of their

food products prior to labelling a food product with a precautionary statement. From the point of view of a manufacturer, once they receive the raw material, they will review the product information form (PIF) which provides specification of other information from the supplier for each ingredient. A decision is then made for each cross-contact allergen if it is present in the final product in a Readily Dispersible form (a powder or liquid in a homogenous form) or Particular form (a separate and distinct particle of material e.g. sesame seed). At this stage, the manufacturer will review the manufacturing line and environment to determine whether there are any cross contact allergens which may become incorporated into the product in the manufacturing process. Examples where cross contact allergens can become incorporated into the product in the manufacturing process are in the mixing bowl, conveyor belts, baking tins and possible incorporation due to shared tools and people (48).

The manufacturer will carry out a risk assessment by entering the above information into the VITAL calculator which has been designed to alert the manufacturer of the possible presence of cross contamination in the final product in the form of action levels. VITAL was first developed in 2005 by the Australian Food and Grocery Council and is now managed by the Australian Allergen Bureau. When first introduced, VITAL 1.0 contained three action levels. Action level 1 was the green zone: if any allergen fell into this zone by an equal or lesser reading, the product contained no labelling; action level two was the yellow zone: if any allergen that fell into this zone by an equal or greater reading than this level, the product had to be labelled with VITAL's "may be present" statement. The last

of the zones was the red zone: with any allergen that had a reading of equal to or greater than this level, the process required was that the allergen be listed as an ingredient (see Table 3).

Table 3: VITAL 1.0 action levels

	Allergen Milk	Egg	Soy	Fish	Peanuts	Tree nuts	Sesame	Crustacea	Gluten
Action level 1 (ppm)	<5	<2	<10	<20	<2	<2	<2	<2	<20
Action level 2 (ppm)	5 - 50	2 - 20	10 - 100	20 - 200	2 - 20	2 - 20	2 - 20	2 - 20	20-100
Action level 3 (ppm)	>50	>20	>100	>200	>20	>20	>20	>20	>100

This information was sourced from the Allergen Bureau website (48)

The process has recently been revised as VITAL 2.0. It now contains two action levels (Figure 2). If an item falls within action level 1 it requires no precautionary statement, however if the product falls within action level 2, VITAL’s “may be present” statement is to be used (VITAL action level 2 is used for allergens in particulate and readily dispersible forms and the total protein concentration from the allergen source is determined and labelled accordingly). In the case of peanut, the action level 1 is currently set at <0.2mg of peanut protein (Table 4). The action levels were developed using the most up to date scientific literature with an independent scientific panel (74-76). A limitation of the VITAL process is that there is no information on food products that contains the “may be present” statement to alert the consumer that this form of labelling is different to traditional precautionary statements. In addition the VITAL 2.0 risk assessment tool does not incorporate routine ELISA allergen testing for confirmation of presumed levels of cross contamination.

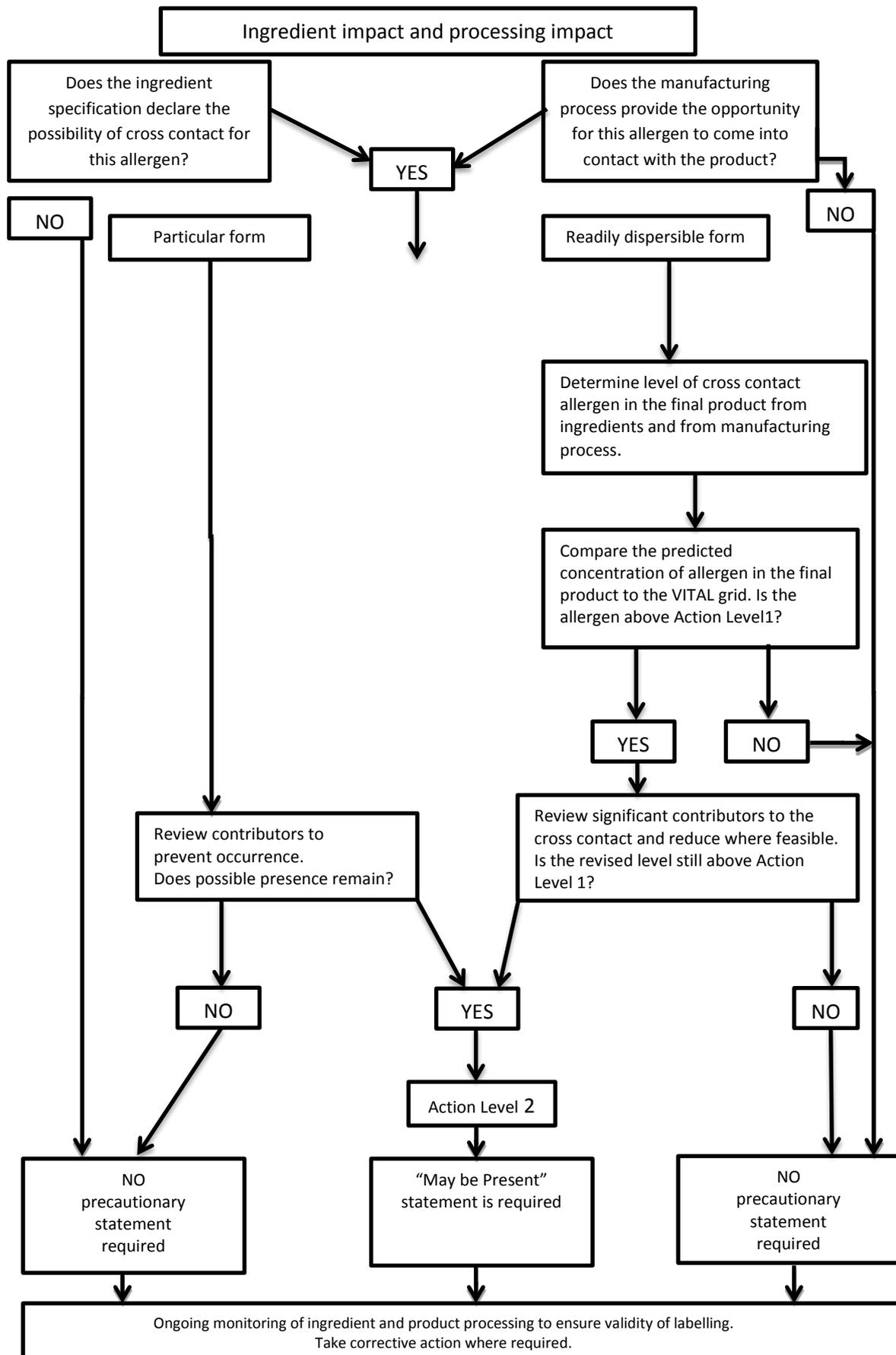
Table 4: VITAL 2.0 reference dose

Allergen name	(short title)	Reference dose (mg of protein)
Almonds & their products	Almond	0.1
Brazil nuts & their products	Brazil nut	0.1
Cashews & their products	Cashew	0.1
Hazelnuts (filberts) & their products	Hazelnuts	0.1
Macadamia nuts & their products	Macadamia nut	0.1
Pecans & their products	Pecan	0.1
Pine nuts (pignolias) & their products	Pine nut	0.1
Pistachio nuts & their products	Pistachio nut	0.1
Walnuts & their products	Walnut	0.1
Wheat or its derivatives or hybridised strains	Wheat	1
Rye or its derivatives or hybridised strains	Rye	1
Barley or its derivatives or hybridised strains	Barley	1
Oats or its derivatives or hybridised strains	Oats	1
Spelt or its derivatives or hybridised strains	Spelt	1
Egg & egg products	Egg	0.03
Crustacea & its products	Crustacea	1
Finfish and finfish products (excluding molluscs)	Fish	0.1
Milk & milk products	Milk	0.1
Peanut & peanut products	Peanut	0.2
Sesame seeds & sesame seed products	Sesame seed	0.2
Soybeans & soybean products	Soy	1
Lupin & lupin products	Lupin	4
Mustard & mustard products	Mustard	0.05

This information was sourced from the Allergen Bureau website (48).

For further discussion of VITAL please see the manuscript entitled, “Hidden Allergens in Food and Implications for Labelling and Clinical Care of Food Allergic Patients” in chapter 8 of this thesis. No study to date has investigated consumer perception regarding precautionary labelling, levels of cross-contamination of processed foods that contain precautionary labelling and the impact of the VITAL process on the manufacturing industry.

Figure 2: VITAL 2.0 decision tree



This information was sourced from the Allergen Bureau website (48).

3.6: Oral food challenges and the development of thresholds for the allergic consumer

A zero tolerance for the offending food creates enormous practical problems for the food industry and is currently unachievable in any case. There is evidence to suggest that threshold levels below which reactions are not provoked in allergic individuals do exist but coming to an agreement on these levels is proving very difficult within the scientific community. A major part of the challenge is that threshold levels are currently based on OFC results (70).

The gold standard for diagnosing food allergy is the OFC, however currently oral food challenges are for the diagnosis of allergy or the development of tolerance. Because these challenges are multiple doses, a clinician cannot be sure about whether a patient is reacting to the first dose administered or, for example, the 3rd dose, if the reaction takes place >45 minutes into the challenge. Interpretation of data for OFC protocols that use graded, incremental doses administered at fixed time intervals, in carefully selected patients is complicated by several factors, including whether a reaction is occurring to a discrete threshold dose of allergen or to the cumulative dose consumed to the point where the challenge is discontinued. As dosing schedules are usually every 15-20 minutes and reactions may occur up to 1 hour after ingestion, a reaction might be related to any of the previous individual doses.

Taylor et al. (2002) sought to determine whether the quality and quantity of existing clinical data on threshold doses for commonly allergenic foods were sufficient to allow consensus to be reached on establishment of threshold doses. The author invited interested parties to participate in a round table conference to share existing data on

threshold doses. In France, clinical data on 306 patients who underwent an OFC for peanut allergy and 281 for egg allergy revealed that the lowest provoking dose for peanut and egg was 1mg. In Australia, clinical data on 299 patients who underwent an OFC for milk allergy showed that the lowest provoking dose for milk was 0.02ml. However a limitation of the data from Australia may have been that different forms of cow's milk were used in the OFC such as liquid cows' milk, non-fat dry milk, and infant formula. This may have made the results difficult to interpret (70). Another limitation is that the OFC was undertaken for diagnostic purposes rather than for determination of the threshold dose and different protocols were used in the various clinics where the data was generated. The author concluded by recommending that international efforts be undertaken to establish threshold doses for commonly allergenic foods using standardised clinical challenge protocols.

Recently Allen et al. (2014) aimed to establish reference doses for commonly allergenic foods. Reference doses were developed from statistical dose-distribution modeling of individual thresholds of patients of more than 55 studies of OFC. The authors results showed that the eliciting dose for an allergic reaction in 1% of the population were estimated as 0.2 mg of protein for peanut, 0.1 mg for cow's milk, 0.03 mg for egg, and 0.1 mg for hazelnut. These reference doses will form the basis of the revised VITAL 2.0 thresholds now recommended in Australia (77) A limitation of this study is that the derived reference doses are based on controlled clinical challenge trials, this would differ from community exposures experienced by patients with food allergy.

3.7 The state of play of precautionary labelling internationally

The use of mandatory declarations on processed foods by manufacturers is similar around the world with the exception of Japan (Table 5). In 2002, as for many other

countries, mandatory food allergy labelling became regulated under Japanese law. The Japanese law mandates precautionary labelling for egg, milk, wheat, buckwheat, peanut, shrimp/prawn and crab. In addition, the law recommends (but does not mandate) the labelling of any food that contains abalone, squid, salmon, roe, orange, kiwifruit, beef, walnut, salmon, mackerel, soybean, chicken, banana, pork, matsutake mushroom, peach, yam, apple and gelatine. In contrast to other countries, the use of precautionary labelling (“may contain xxx”) in Japan is strictly prohibited (78).

The Japanese government has also established a threshold for food allergy labelling and designated 10 mg protein/g food as a threshold to monitor labelling using ELISA (Table 6). This is to say that if any trace amounts of food protein are detected greater than 10 mg protein/g, labelling of that allergen is necessary and only then should the food product contain a statement to alert the consumer that trace amounts of that specific allergen are present. However if trace amounts are found lower than the designated threshold amount, no labelling is allowed as it is deemed unnecessary (78). In contrast, the Swiss legislation regarding the warning of cross contamination is that foods must only be declared when they have been added involuntarily, with a level of more than 1g/kg of allergen or in excess of 10 mg per kilogram. For sulphites, any trace amount lower than this does not require any mandatory or voluntary labelling (79) (Table 6).

The Ministry of Health, Labour and Welfare (MHLW) of Japan has provided a definition of a trace amount and is regulating this by law. In doing so, the Japanese government has recognised that zero tolerance of the offending food is unrealistic and would cause an enormous practical problem (78).

However, little is known of the frequency and type of reactions resulting from consumption of foods with this current definition. This data would help to validate Japan's definition of trace amounts as well as the assumption that levels below this threshold are not harmful.

Korean law states that the names and quantities of raw materials that are known to cause allergy amongst Koreans which have been deliberately added to food components (or if food components were obtained through extraction) must be labelled regardless of their quantities. These foods include eggs, poultry meat, milk, buckwheat, peanuts, soybeans, wheats, mackerels, crabs, pork, peaches and tomatoes (80) (Table 5, 6).

Singaporean law requires the declaration of foods also known to cause allergy. These are cereals, crustacea, eggs, fish, peanut, milk, tree nuts and soy. The use of the statement "may contain" is discouraged; those manufacturers who choose to use these statements must provide justification of these statements if consumers raise any concerns about the presence of potential food allergens (Table 5, 6) (81). Other countries around the globe allow manufacturers to voluntarily use precautionary statements on processed foods in conjunction with a good manufacturing process and the manufacturer's choice of a risk assessment tool (Table 6).

The Codex Alimentarius Commission, established by the World Health Organisation (WHO) and the Food and Agriculture Organisation of the United Nations (FAO) in 1963 developed international food standards, guidelines and codes of practice to protect the health of consumers and to ensure fair and safe labelling of ingredients that cause severe allergic reactions (82).

The Argentinean government follows the Codex recommendation for mandatory food labelling, however they have included Tartrazine which is used for food colouring as a product that must be labelled along with food allergens. Precautionary statements such as “may contain traces of...” in Argentina are prohibited. Manufacturers are encouraged to label food products with “contains” even if they are not sure that such traces are actually in the food product (83, 84) (Table 5,6).

Other countries such as Bolivia, Chile, Colombia, Costa Rica, Cuba, Mexico, Nicaragua and Venezuela also follow the Codex recommendation (or a slight alteration) for mandatory food labelling (Table 5).

As mentioned previously, mandatory food labelling of allergens that may cause reaction in susceptible individuals is governed by law in most countries around the world. However, despite an exhaustive investigation of the current literature available concerning the practice of precautionary labelling in the above-mentioned countries, no information was available on their current practice. Of the documents that were available, none outlined any laws that forbid the use of precautionary statements. Therefore in the absence of any law, the assumption was made that this practice is currently in use in those countries.

Table 5: International comparison of mandatory declarations on processed foods

Country	Peanuts	Tree nuts	Egg	Milk	Fish	Crustaceans	Sesame	Soy	Cereals	Celery	Mustard	Lupin	Molluscs	Buckwheat	Shrimp	Crab	Wheat	Sulphites
USA	√	√	√	√	√	√		√	√									√
*ANZ	√	√	√	√	√	√	√	√	√									√
Canada	√	√	√	√	√		√	√	√									√
EU	√	√	√	√	√	√	√	√	√	√	√	√	√					√
Japan	√		√	√						√				√	√	√	√	
Codex	√	√	√	√	√	√		√	√									
Korea	√	√	√	√	√	√			√									√
Singapore	√	√	√	√	√	√		√	√									√
Hong Kong	√	√	√	√	√	√		√	√									√
Argentina	√	√	√	√	√	√		√	√									√
Bolivia	√	√	√	√	√	√		√	√									√
Chile	√	√	√	√	√	√		√	√									√
Colombia	√	√	√	√	√	√		√	√									√
Costa Rica	√	√	√	√	√	√		√	√									√
Cuba	√	√	√	√	√	√		√	√									√
Mexico	√	√	√	√	√	√		√	√									√
Nicaragua	√	√	√	√	√	√		√	√									√
Venezuela	√	√	√	√	√	√		√	√									√

*ANZ = Australia and New Zealand. (80, 83, 85-92).

Table 6: International comparison of voluntary declarations on processed foods

Country	Precautionary statements such as “may contain” in current practice	No precautionary statements in use	Threshold cut-off points for these countries
U.S.A	√		
EU	√		
Switzerland		√	1g/kg of allergen
Japan		√	10 mg protein/g
ANZ*	√		
Canada	√		
Korea	√		
South Africa	√		
Singapore	√		
Hong Kong	√		
Argentina		√	Nil
Mexico	√		
Chile**	√		
Colombia**	√		
Costa Rica**	√		
Cuba**	√		
Bolivia**	√		
Nicaragua**	√		
Venezuela**	√		

*ANZ = Australia and New Zealand. **There is no law that forbids the use of precautionary statements. The assumption was made that this practice is currently in use in these countries (79-81, 83, 85, 89-93).

Aims

The aims of this project are four fold:

Aim 1

To investigate the proportion of products with any precautionary labelling in an Australian supermarket with any of the 9 most common allergens (peanuts, tree nuts, egg, milk, sesame, crustaceans, fish, wheat and soy) and to examine the impact of the VITAL process on the manufacturing industry and its uptake within Australian supermarkets.

Aim 2

To investigate whether consumers with a history of anaphylaxis in Australia are ignoring precautionary statements and whether they believe that these statements only protect the manufacturer from litigation.

Aim 3

To examine the level of cross contamination with processed foods known to have a high prevalence of precautionary labelling containing peanut, hazelnut, milk, egg, soy and lupin. This examination will be carried out in three different Australian supermarkets (Woolworths, Coles and Aldi).

Aim 4

To investigate the safety and acceptance of a prospective single dose oral food challenge study of peanut allergen thresholds in the Australian setting.

Hypothesis

I hypothesise that precautionary labelling in an Australian supermarket for any of the 9 most common allergens is high and that the impact of the VITAL process on the manufacturing industry and its uptake within Australian supermarkets is low since its establishment in 2005.

I also hypothesise that consumers with a history of anaphylaxis in Australia are ignoring precautionary statements and believe that these statements only protect the manufacturer from litigation.

In addition I hypothesise that the level of cross contamination in processed foods for peanut, hazelnut, milk, egg, soy and lupin with precautionary statements in Australian supermarkets is low.

Finally I hypothesise that prospective single dose oral food challenge studies of peanut allergen thresholds are both safe and acceptable to be performed within the Australian setting.

Chapter 4: General materials and methods

This section describes the general materials and methods used in the thesis by publication. Further descriptions of the procedures can be found in Chapters 5 - 9 of this thesis.

4.1 Precautionary allergen labelling following new labelling practices in Australia

In chapter 5, a large supermarket in metropolitan Melbourne was contacted and permission was obtained to investigate the use of precautionary labelling for peanuts, tree nuts (of any kind), eggs, milk, sesame, crustaceans, fish, wheat, soy and lupin on packaged processed goods in supermarket products. The following categories of products were examined: sweet biscuits; breakfast cereals; savoury biscuits; noodles/rice/Asian foods; pasta and pasta sauce, soups and canned meals; prepared meals (including Indian meals, Mexican foods and side dishes); dinner bases (including batters and stocks); cake mixes (including cupcakes, cakes, muffins, cookies and pancakes); bakery products (including bread and bread crumbs); baby food; confectionery (including chewing gum), chocolate bars or blocks and desserts. Results were entered into a data sheet and percentages were calculated.

4.2 Consumer perceptions of precautionary labelling in families with food allergy and anaphylaxis in Australia

Chapter 6 describes a questionnaire-based study of a consecutive series of 497 parents of children attending the Department of Allergy at The Royal Children's Hospital, Melbourne, Australia. This was undertaken between August-October 2011 with a 93% response rate. The study was approved by the Royal Children's Hospital Human

Research Ethics Committee (RCH HREC 31140A). All parents who had appointments for their child to undergo a Skin Prick Test (SPT) were given the opportunity to participate. Analyses were restricted to parents of children with an existing doctor diagnosis of food allergy (n=293) and responses were compared between those with a history of anaphylaxis and those with a history of mild to moderate allergic reactions. The questionnaire was focused on gaining a greater understanding of the attitudes of parents with children who may or not have food allergies. It investigated their understanding of precautionary labelling and its perceived usefulness as well as discovering the changes that consumers would like to see being made to precautionary labelling. A non-responder questionnaire was also designed to allow comparison with those who chose to participate and those who chose not to (Appendix 2).

4.3 Foods with precautionary allergen labelling in Australia rarely contain detectable allergen

Chapter 7 examines the level of cross contamination for peanut, hazelnut, milk, egg, soy and lupin in 135 “private label” processed foods with precautionary statements by visiting three different Australian supermarkets (Woolworths/Safeway, Coles and ALDI). In total, 128 samples were obtained from three different Australian supermarkets to undergo allergen content analysis by Enzyme-Linked Immuno Sorbent Assay (ELISA) for peanut, hazelnut, milk, egg, soy and lupin protein. The laboratory was blinded to the labelling and supermarket origin of products.

In total, 768 ELISAs were performed using commercial Neogen Veratox™ kits. The lower limit of detection was 2.5 ppm of total allergen ($\mu\text{g per g}$) for each food. Our purchasing strategy included five categories of food products to be analysed, namely chocolates, breakfast cereals, muesli bars, savoury biscuits, and sweet biscuits. These

products were found in our own study to carry a high level of precautionary labelling. The selection of chocolates allowed comparison with a previous European study.

For each of the five categories we chose 3 variations to ensure that we covered a range of products within the specific category. Also, we limited our analysis by only selecting private labelled products (these are supermarkets' own brands which are usually less expensive) being as these products were more likely to have undergone the VITAL process.

We chose to analyse food products for cow's milk, egg and peanut proteins as these allergens are most commonly associated with food allergy in Australian children (4). The analysis of cashew nut was not undertaken as there were no commercial kits available at the time of this study. In our analysis we chose to include hazelnut to compare our finding with European studies as hazelnut is most commonly analysed within these studies. We also included soy and lupin as soy is often used in food products, is ubiquitous in the food manufacturing chain, and is not a common cause of food allergy. Lupin was also included as it has been recommended by Food Safety Australia New Zealand (FSANZ) as possibly the next allergen requiring labelling and is an emerging allergy particularly in Europe where it is commonly used in the food chain. We also had a discussion regarding testing for macadamia nut and sesame seed. We chose to exclude these from our analysis as macadamia is not a common food allergen and sesame is usually present in food products in the form of seeds, therefore it would be difficult to determine trace contamination.

The study was funded by the Food Allergy Research & Resource Program (FARRP) in the US. FARRP provided the ELIZA kits and Food Allergen Control Training Analysis (FACTA) performed the analysis.

4.4 Hidden allergens in foods and implications for labelling and clinical care of food allergic patients

In chapter 8, a detailed search was undertaken to examine the current literature regarding precautionary labelling, consumer behaviours and attitudes regarding this type of labelling, risk to the consumer, the analytical results of products that bear advisory labelling, the current debate regarding whether a tolerable level of risk can be obtained in food allergy and the newly introduced Voluntary Incidental Trace Allergen Labelling (VITAL) system in Australia.

4.5 Peanut Allergen Threshold Study (PATS): validation of eliciting doses using a novel single-dose challenge protocol

Chapter 9 describes the estimation of the population threshold for allergic reactions in peanut allergic subjects. This has been estimated at 1.5 mg of peanut protein. This has potential value for public health measures. The paper outlines the methods for the validation of reaction, eliciting doses of peanut using a novel single dose protocol that may assist in developing an objective risk assessment tool for peanut allergic consumers. The study was a multi-centre study involving these teaching centres: University Hospital UCC Cork; the Royal Children's Hospital Melbourne, Australia; the General Hospital, Food Allergies Centre, Massachusetts and the General Hospital, Boston, U.S.A. A total of 375 participants were recruited during their follow-up appointments in the Department of Allergy in each respective centre. The aim was to

assess the precision of the predicted EDO5 using a single dose (6mg peanut = 1.5mg of peanut protein) in the form of a cookie. Validated Food Allergy related Quality of Life Questionnaires (FAQLQ) were available for all age groups and were self-administered prior to the OFC and 1 month after the challenge.

Chapter 5: Precautionary allergen labelling following new labelling practice in Australia

Introduction

Chapter five examines the prevalence of precautionary allergen labelling following the introduction of new labelling practices in Australia.

The paper entitled, “Precautionary allergen labelling following new labelling practice in Australia” by Giovanni A Zurzolo, Michael L Mathai, Jennifer J Koplin and Katrina J Allen was published in the peer reviewed journal, *The Journal of Paediatrics and Child Health*, 2013; 49 (4): E306-10.

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It is available from: <https://doi.org/10.1111/jpc.12138>

PART B:
DECLARATION OF CO-AUTHORSHIP AND CO-CONTRIBUTION: PAPERS INCORPORATED IN THESIS BY PUBLICATION

This declaration is to be completed for each conjointly authored publication and placed at the beginning of the thesis chapter in which the publication appears.

Declaration by Giovanni Zurzolo

Signature:



Date:

6/6/2013

 Paper Title: Precautionary allergen labeling following new labeling practice in Australia

In the case of the above publication, the following authors contributed to the work as follows:

Name	Contribution%	Nature of contribution
Giovanni Zurzolo	65	Survey of food products Evaluated analytical data Performed statistical analysis Prepared major part of the manuscript
Dr Jenifer Koplin	10	Assisted in statistical analysis Provide input in direction of manuscript
Prof Katie Allen	20	Designed study Interpreted data Assisted with manuscript preparation Approved final version
Prof Michael Mathai	5	Provide input Read final submission

DECLARATION BY CO-AUTHORS

The undersigned certify that:

1. They meet criteria for authorship in that they have participated in the conception, execution or interpretation of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. There are no other authors of the publication according to these criteria;
4. Potential conflicts of interest have been disclosed to a) granting bodies, b) the editor or publisher of journals or other publications, and c) the head of the responsible academic unit; and
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Signature 4	[Redacted]	6/6/2013

Chapter 6: Perceptions of precautionary labelling among parents of children with food allergy and anaphylaxis

Chapter six examines the perception of precautionary labelling among children with food allergy.

The paper entitled, “Perceptions of precautionary labelling among parents of children with food allergy and anaphylaxis” by Giovanni A Zurzolo, Jennifer J Koplin, Michael L Mathai, Mimi Tang and Katrina J Allen was published in the peer reviewed journal, *The Medical Journal of Australia*, 2013; 198 (11): 621-3.

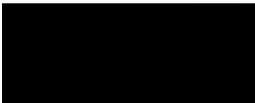
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Paper Title: Consumer perceptions of precautionary labeling in families with food allergy and anaphylaxis in Australia

In the case of the above publication, the following authors contributed to the work as follows:

Name	Contribution%	Nature of contribution
Giovanni Zurzolo	65	Ethics application Devolvement of questionnaire Recruitment Evaluated analytical data Performed statistical analysis Prepared major part of the manuscript
Dr Jenifer Koplin	11	Assisted in statistical analysis Provide input in direction of manuscript
Prof Katie Allen	20	Designed study Interpreted data Assisted with manuscript preparation Approved final version
Prof Michael Mathai	2	Provide input Read final submission
A/Prof Mimi Tang	2	Provide input in direction of manuscript

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Signature 4	[Redacted]	6/6/13
Signature 5	[Redacted]	5/6/13

Chapter 7: Foods with precautionary allergen labelling in Australia rarely contain detectable allergen

Chapter seven examines the prevalence of trace contamination of products that bear precautionary allergen labelling in Australia.

The paper entitled, “Foods with Precautionary Allergen Labelling in Australia Rarely Contain Detectable Allergen” by Giovanni A. Zurzolo, Jennifer J. Koplin, Michael L. Mathai, Steve L. Taylor, Dean Tey, and Katrina J. Allen was published in the peer reviewed journal called *The Journal of Allergy and Clinical Immunology: In Practice* 2013; 1 (4): 401-6.

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Declaration by Giovanni Zurzolo

Signature:



Date:

6/6/2023
Paper Title: Foods with Precautionary Allergen Labeling in Australia Rarely Contain Detectable Allergen

In the case of the above publication, the following authors contributed to the work as follows:

Name	Contribution%	Nature of contribution
Giovanni Zurzolo	65	Ethics application Devolvement of questionnaire Acquired funding from FACTA & FARRP Recruitment Evaluated analytical data Performed statistical analysis Prepared major part of the manuscript
Dr Jenifer Koplín	10	Assisted in statistical analysis Provide input in direction of manuscript
Prof Katie Allen	20	Designed study Interpreted data Assisted with manuscript preparation Approved final version
Prof Steve Taylor	2	Provide input in direction of manuscript
Dr Dean Tey	2	Assisted in statistical analysis
Prof Michael Mathai	1	Provide input Read final submission

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Signature 3		5/8/13
Signature 4		24/6/13
Signature 5		6/5/13
Signature 6		6/6/13

Clinical Communications

Foods with precautionary allergen labeling in Australia rarely contain detectable allergen

Giovanni A. Zurzolo, BMedSc (Hon)^{a,b},
Jennifer J. Koplin, PhD^a, Michael L. Mathai, PhD^b,
Steve L. Taylor, PhD^c, Dean Tey, MD^{a,d,e}, and
Katrina J. Allen, MD, PhD, FAACAAI^{a,d,e}

Clinical Implication

- Ingestion of products with precautionary labeling is low risk except for consumers with peanut allergy. A reporting system to catalog and investigate adverse reactions to foods with precautionary labeling is advised.

TO THE EDITOR:

In 2008, we undertook a survey of food products that carried precautionary labeling within the Australian supermarket setting.¹ We then repeated the same survey in 2011 to examine changes in the prevalence of precautionary labeling over a 3-year period. Our results showed that overall 65% of products contained 1 or more precautionary statements to any of the nine most common food allergens (peanuts, tree nuts, egg, milk, sesame, crustaceans, fish, wheat, and soy).²

We also have recently examined consumers' behavior, perceptions, and opinions about precautionary labeling, which showed that even those with a history of anaphylaxis to food appeared to be complacent for avoidance of foods with precautionary labeling, perhaps because of their ubiquity or because the perceived risks are low.³

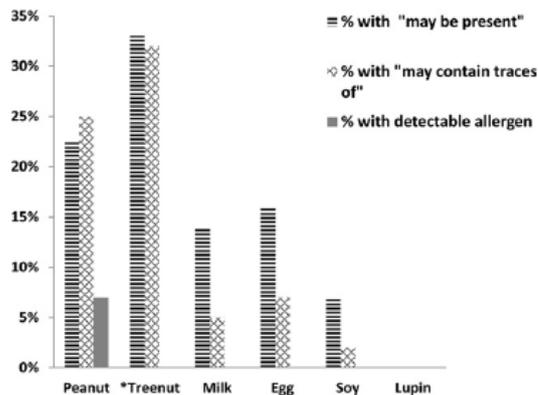


FIGURE 1. Results for analysis of processed food with precautionary labeling. Shown is the percentage of the 128 examined foods that contained precautionary labeling for each allergen and the percentage of products that had detectable allergen present. *Hazelnut (n = 5) was the only specific tree nut for which ELISA testing was performed.

In most countries labeling information is covered by legislation. In 2003, food labeling legislation was introduced in Australia and New Zealand, followed by similar legislation introduced by the European Commission and the US Congress in 2003-2004.⁴⁻⁶ Australian legislation requires mandatory labeling of the most common allergenic foods: peanuts, tree nuts, milk, eggs, sesame, fish, crustaceans, soy, and gluten, as well as ingredients derived from those foods. Other nations have similar legislation in place for these allergens; however, no legislation currently covers precautionary labeling.⁴

In this present study we aimed to examine the level of cross-contamination for peanut, hazelnut, milk, egg, soy, and lupin in 135 "private label" processed foods with precautionary statements by visiting three different Australian supermarkets (Woolworths, Coles, and Aldi) to assess the risks taken by allergic consumers choosing to ignore precautionary labeling in the Australian setting. The first two supermarket chains represent a commercial duopoly that provide 80% of Australian supermarket products,⁷ with a third selected which has recently entered the Australian market from Europe and may therefore be reflective of European manufacturing procedures.

We examined five categories of high-risk foods, defined by the high level of precautionary labeling and clinical knowledge of foods most likely to be contaminated, namely chocolates, breakfast cereals, muesli bars, savory biscuits, and sweet biscuits (cookies). Greater than 70% of these products were found in our previous studies to carry precautionary labeling.^{1,2}

Products were selected as follows. First, three products were chosen within each of the above categories (eg, three different types of muesli bar). All products chosen were private label products. The assumption was made that all products having the "may be present" statement had been through the Voluntary Incidental Trace Allergen Labeling (VITAL) process. The VITAL procedure encourages manufacturers to undergo a more intensive investigation into the possible presence of allergens before their release to consumers. It also uses a new precautionary statement: May be Present. VITAL also allows evaluation of the possible amount of cross-contamination with the use of an interactive action level grid: if the level of cross-contamination is equal to or above the action level then VITAL's may be present statement is used as a precautionary statement to replace all other precautionary statements; if it is below the action level concentration, then no precautionary labeling is required. A more detailed description of the VITAL process has been published previously.² Second, for each product, samples were obtained from each of the three supermarket chains (eg, private label chocolate chip muesli bars were purchased from Woolworths, Coles, and Aldi). Third, three batches were purchased for each product from each of the three supermarket chains (eg, three batches of private label chocolate chip muesli bars from Woolworths).

In total, 128 samples were obtained (eight products were not available on the day of selection). Several different precautionary statements were used: may be present (n = 67; 53%), may contain (n = 56; 44%), and no statement (n = 4; 3%). Samples underwent analysis by enzyme-linked immunosorbent assay (ELISA) with the use of commercial Neogen Veratox kits that measured total protein content of each of the allergens (peanut, hazelnut, milk, egg, soy, and lupin). In total, 768 ELISAs were

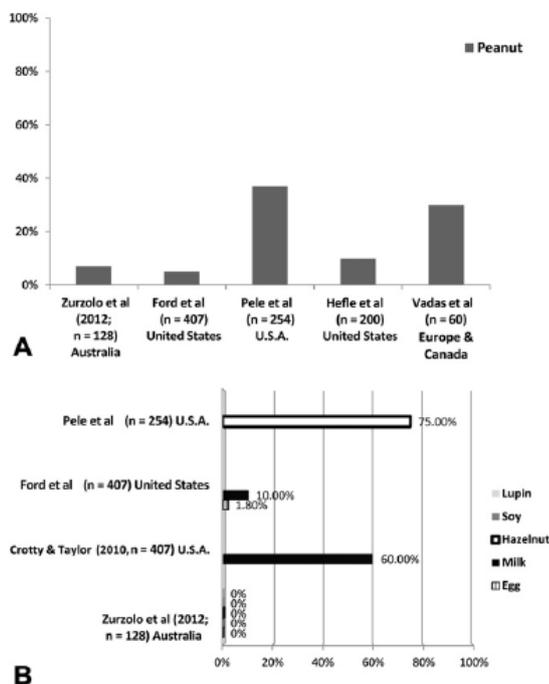


FIGURE 2. Shown is a comparison of our results with those of other studies that investigated cross-contamination with (A) peanut and (B) other foods. Crotty and Taylor¹⁰ analyzed products for milk only. Ford et al¹¹ analyzed products for peanut, egg, and milk only. Pele et al¹² analyzed products for peanut and hazelnut only.

performed. The laboratory was blinded to the labeling and supermarket origin of products. The lower limit of detection was 2.5 ppm ($\mu\text{g/g}$) of total allergen.

Of the 128 samples, only nine (7.0%) with precautionary labeling had detectable levels of peanut with concentrations ranging from >2.5 ppm to <50 ppm for whole peanut or >0.63 ppm to <12.5 ppm for peanut protein. None of these products had been through the VITAL process. Of all other samples that had precautionary labeling for hazelnut, milk, egg, soy, or lupin, none were found to have any detectable level of those allergens (Figures 1 and 2).

The nine samples with detectable levels of peanut came from three unique products, with all three batches of each product containing varying levels of peanut. Chocolate biscuits fruit and nut contained 12 to 30 ppm of whole peanut (or 3-7.5 ppm of peanut protein). Yogurt strawberry muesli bar contained 4 to 20 ppm of whole peanut (or 1-5 ppm of peanut protein). Choco swirl muesli bar contained 30 to 50 ppm of whole peanut (or 7.5-12.5 ppm of peanut protein).

Of these 9 samples, 100% were below the estimated dose to which 5% of persons with peanut allergy are expected to react of 1.5 mg of peanut protein calculated by Taylor et al⁸ when the above levels of contamination were converted to milligrams with the use of the recommended serving size for each product (these ranged from 17 to 31 g).

The key strengths of this study are that we analyzed food products from three different supermarkets that represent both

the Australian and European industry. We tested three samples of each product. Each sample came from a product purchased from a different supermarket within each chain, with each purchase taking place at a supermarket in a different location. Previous studies have analyzed fewer samples for each product.

Our study is the first to investigate cross-contamination by soy or lupin. Labeling of foods containing lupin is not currently mandatory in Australia; however, it has been included in the present study because it is an emerging allergy, particularly in Europe where it is more commonly used in the food chain. Food Safety Australia New Zealand is currently investigating lupin allergy in Australia to determine whether labeling for lupin is required. The benefits of precautionary labeling for soy are unclear, given that soy is an uncommon cause of death from food-related anaphylaxis, and threshold doses for reaction to soy have not been well established.

The limitations of this study include a reasonably small selection of goods, although we enriched for products that from our previous supermarket survey, and the published literature had a high rate of labeling and potential contamination. In addition, we cannot exclude the possibility that different batches of these same products might have contained higher levels of the allergen. Another limitation may have been that we did not assess foods for the presence of tree nuts with the exception of hazelnut; further studies are needed to address this.

European and US studies have also investigated allergen content in processed foods.⁹ Crotty and Taylor¹⁰ examined 100

food products with precautionary labeling for milk. They found that 60% of products contained milk residues that ranged from 3 to 4000 ppm.¹⁰ In a broader survey of products that had precautionary statements for either egg, milk, or peanut, Ford et al¹¹ found detectable residues of egg in 1.8% (6 ppm), milk in 10.2% (4-22 ppm), and peanut in 4.5% (5-161 ppm). Furthermore, Pele et al¹² analyzed 254 chocolate products for peanut and found that 37% of products had peanut traces. Hefle et al¹³ analyzed 200 products and found that 10% of those bearing advisory statements had peanut traces.

Such differences between those studies can be expected when manufacturers in most countries are not using standardized risk assessment tools such as VITAL and are instead making variable decisions about the necessity of applying precautionary labeling statements.

In our present study, most products contained no detectable levels of allergen irrespective of whether the allergen in question was listed in a precautionary statement, suggesting that risk currently being taken by Australian allergic consumers is probably low except in the context of peanut allergy. Even when peanut contamination was present, it is unlikely that the dose of peanut detected in our study would cause a reaction in most of the peanut allergic community.⁹

Importantly, no trace allergens (including peanut) were found in products that had been through the VITAL 1.0 process. This suggests that there may be an overuse of precautionary labeling even when the VITAL process has been used. The new VITAL 2.0, which has raised the threshold for reporting, may improve the correct use of precautionary labeling. Currently, VITAL has endorsed training taken place in Australia, New Zealand, Netherlands, Belgium, South Africa, Germany, and Norway. Further information on this training is available at the VITAL Website.¹⁴

The findings of this present study, in conjunction with previous research showing that precautionary labeling is ubiquitous^{1,2} and is often ignored,³ suggest that consumers may not be undertaking substantial risk in their ingestion of these products. Future research should investigate the frequency and type of reactions that result from consumption of foods with precautionary labeling, in the current regulatory climate where precautionary labeling is voluntary. A national reporting system to catalog and investigate adverse reactions to foods with precautionary labeling would provide important confirmatory information about the effect of food labeling on consumer outcome.

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Chapter 8: Hidden allergens in foods and implications for labelling and clinical care of food allergic patients

Introduction

Chapter eight examines the current literature regarding the risk to the consumer and the analytical results of products that bear precautionary labelling.

The paper entitled, “Hidden allergens in foods and implications for labelling and clinical care of food allergic patients” by Giovanni A Zurzolo, Michael L Mathai, Jennifer J Koplin and Katrina J Allen was published in the peer reviewed journal, *Current Allergy Asthma Reports*, 2012; 12 (4): 292-6.

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PART B:

DECLARATION OF CO-AUTHORSHIP AND CO-CONTRIBUTION: PAPERS INCORPORATED IN THESIS BY PUBLICATION

This declaration is to be completed for each conjointly authored publication and placed at the beginning of the thesis chapter in which the publication appears.

Declaration by Giovanni Zurzolo

Signature:



Date: 6/6/2013

Paper Title: Hidden allergens in foods and implications for labeling and clinical care of food allergic patients

In the case of the above publication, the following authors contributed to the work as follows:

Name	Contribution%	Nature of contribution
Giovanni Zurzolo	65	Literature review Prepared major part of the manuscript
Dr Jenifer Koplin	13	Provide input in direction of manuscript
Prof Katie Allen	20	Provide input in direction of manuscript Assisted with manuscript preparation Approved final version
Prof Michael Mathai	2	Provide input Read final submission

DECLARATION BY CO-AUTHORS

The undersigned certify that:

1. They meet criteria for authorship in that they have participated in the conception, execution or interpretation of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. There are no other authors of the publication according to these criteria;
4. Potential conflicts of interest have been disclosed to a) granting bodies, b) the editor or publisher of journals or other publications, and c) the head of the responsible academic unit; and
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Signature 3		5/5/13
Signature 4		6/6/2013

Chapter 9: Peanut Allergen Threshold Study (PATS): validation of eliciting doses using a novel single-dose challenge protocol

Chapter nine examines the eliciting dose (ED) for a peanut allergic reaction in 5% of the peanut allergic population and assesses the precision of the predicted ED05 dose to discover whether this dose is predictive of an allergic response. The paper entitled, “Peanut Allergen Threshold Study (PATS): validation of eliciting doses using a novel single-dose challenge protocol” by Giovanni A Zurzolo, Katrina J Allen, Steve L Taylor, Wayne G Shreffler, Joseph L Baumert, Mimi L.K. Tang, Lyle C. Gurrin, Michael L Mathai, Julie A Nordlee, Audrey Dunn Galvin and Jonathan O’B Hourihane, was published on September 17th 2013 into the journal: *Allergy, Asthma & Clinical Immunology*, 2013; 9(1):35.

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Paper Title: Peanut Allergen Threshold Study (PATS): validation of eliciting doses using a novel single-dose challenge protocol

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Name	Contribution%	Nature of contribution
Giovanni Zurzolo	65	Ethics application Recruitment Prepared major part of the manuscript
Steve L Taylor	2	Provide input in direction of manuscript
Prof Katie Allen	9	Assisted with manuscript preparation Provide input in direction of manuscript
Wayne Shreffler	3	Provide input in direction of manuscript
Joseph Baumert	3	Revised the manuscript critically for important intellectual content
Mimi L.K. Tang	1	Contributed to refinement of the study protocol and review of manuscript
Lyle Gurrin	3	Reviewed the epidemiological study design, proposed the statistical analysis plan and contributed to the writing and revision of the paper.
Michael L Mathai	1	Provide input in direction of manuscript
Julie Nordlee	1	Contributed to the drafting of the manuscript
Audrey DunnGgalvin	3	Contributed to study design and has contributed in drafting and revising the manuscript
Jonathan O.B Hourihane	9	Substantial intellectual contribution to the manuscript has been involved in drafting and giving final approval of the version to be published.

DECLARATION BY CO-AUTHORS

The undersigned certify that:

1. They meet criteria for authorship in that they have participated in the conception, execution or interpretation of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. There are no other authors of the publication according to these criteria;
4. Potential conflicts of interest have been disclosed to a) granting bodies, b) the editor or publisher of journals or other publications, and c) the head of the responsible academic unit; and
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RESEARCH

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Peanut Allergen Threshold Study (PATS): validation of eliciting doses using a novel single-dose challenge protocol

Giovanni A Zurzolo^{1,2}, Katrina J Allen^{1,3,4}, Steve L Taylor⁵, Wayne G Shreffler⁶, Joseph L Baumert⁵, Mimi L K Tang^{1,3,4}, Lyle C Gurrin⁷, Michael L Mathai², Julie A Nordlee⁵, Audrey DunnGalvin⁸ and Jonathan O'B Hourihane^{8*}

Abstract

Background: The eliciting dose (ED) for a peanut allergic reaction in 5% of the peanut allergic population, the ED05, is 1.5 mg of peanut protein. This ED05 was derived from oral food challenges (OFC) that use graded, incremental doses administered at fixed time intervals. Individual patients' threshold doses were used to generate population dose-distribution curves using probability distributions from which the ED05 was then determined. It is important to clinically validate that this dose is predictive of the allergenic response in a further unselected group of peanut-allergic individuals.

Methods/Aims: This is a multi-centre study involving three national level referral and teaching centres. (Cork University Hospital, Ireland, Royal Children's Hospital Melbourne, Australia and Massachusetts General Hospital, Boston, U.S.A.) The study is now in process and will continue to run until all centres have recruited 125 participants in each respective centre.

A total of 375 participants, aged 1–18 years will be recruited during routine Allergy appointments in the centres. The aim is to assess the precision of the predicted ED05 using a single dose (6 mg peanut = 1.5 mg of peanut protein) in the form of a cookie. Validated Food Allergy related Quality of Life Questionnaires-(FAQLQ) will be self-administered prior to OFC and 1 month after challenge to assess the impact of a single dose OFC on FAQL. Serological and cell based in vitro studies will be performed.

Conclusion: The validation of the ED05 threshold for allergic reactions in peanut allergic subjects has potential value for public health measures. The single dose OFC, based upon the statistical dose-distribution analysis of past challenge trials, promises an efficient approach to identify the most highly sensitive patients within any given food-allergic population.

Keywords: Eliciting dose (ED), Food Allergy related Quality of Life Questionnaires-(FAQLQ), Single dose, Peanut thresholds, Oral Food Challenges (OFC), Voluntary Incidental Trace Allergen Labelling (VITAL), Peanut Allergen Threshold Study (PATS)

Introduction

The eliciting dose (ED) for a peanut allergic reaction in 5% of the peanut allergic population (ED05) has been estimated at 1.5 mg of peanut protein. This ED05 estimate was derived from the statistical dose-distribution of peanut allergic individuals (children and adults). All

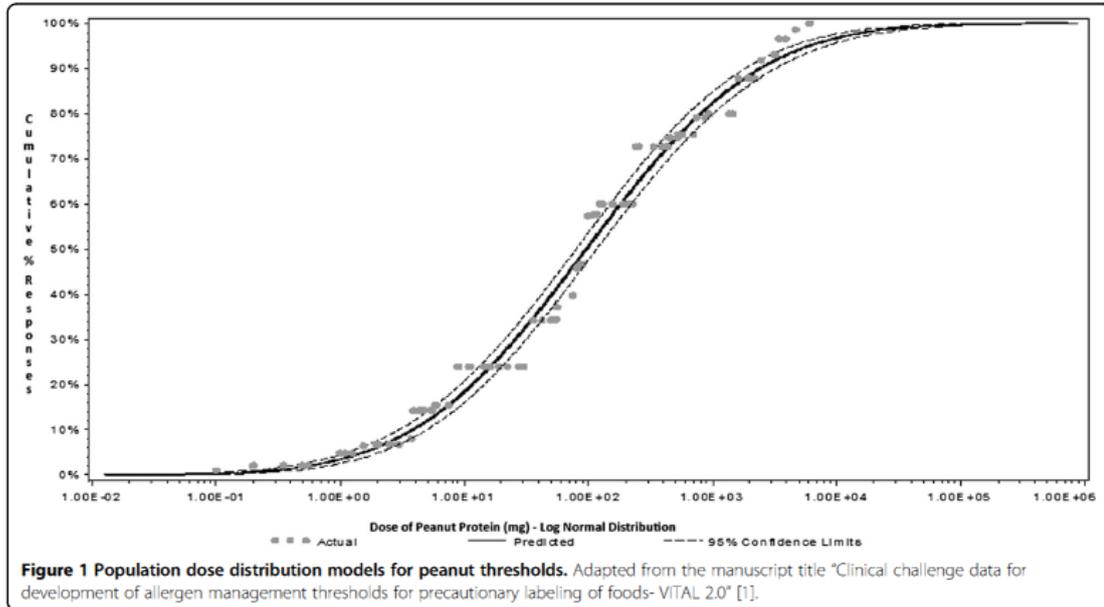
individuals participated in oral food challenge (OFC) protocols that use graded, incremental doses administered at short, fixed time intervals, as shown in Figure 1, with a strong, monotonic relationship between dose and the proportion of study participants reacting at each actual or extrapolated dose [1]. It is not always possible to determine whether a reaction has occurred to a *discrete* threshold dose of allergen or alternatively has been the result of the *cumulative* dose consumed by the allergic

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individual at the time of reaction. Statistical methods can be used to model the dose-distribution of the peanut-allergic population when the precise threshold dose is known to fall within a defined dosing interval but the exact threshold value is unknown [2,3]. Since the ED05 is derived from statistical dose-distribution models of the peanut-allergic population, it is important to clinically validate that this dose is predictive of the allergenic response in a further unselected group of peanut-allergic individuals.

This issue is of importance to all stakeholders in food allergy because over the last 10 years an increasing number of food manufacturers have incorporated voluntary allergen precautionary statements which advise the allergic consumer of the potential presence of allergens using "may contain allergen" statements which are not legislated for and are variable in content around the world [4]. Regulatory thresholds for allergen labelling currently do not exist in most countries, with the exception of Japan and Switzerland. Voluntary industry-led initiatives that use clinical thresholds as the basis for precautionary labelling decisions are based on ED estimates derived from multiple dosing food challenges. Although attempts to improve labelling have been introduced in some countries (e.g. Australia with Voluntary Incidental Trace Allergen Labelling VITAL 2.0), these are still hampered by being voluntary and currently are considered to lack credibility [5].

This study aims to assess the precision of the predicted ED05 using a single dose (6 mg peanut = 1.5 mg of peanut protein, approximately 1/100th of a peanut

kernel) challenge and to validate the modelling that has been used to develop precautionary labelling criteria for VITAL 2.0, as currently VITAL 2.0 uses ED01 (0.2 mg of peanut protein) to estimate its reference doses [6]. In addition this study will examine whether 95% of peanut-allergic consumers are tolerant of an amount that is more than 5 times higher than the VITAL ED01 threshold, thus suggesting if 95% of participants are tolerant to an ED05 then there would be an exceedingly low probability that they would react to an ED01. The ED05 has been chosen pragmatically as it will allow the study to proceed with the recruitment of an achievable number of peanut-allergic individuals to provide sufficient statistical power to validate the accuracy of the population threshold distribution of peanut allergic individuals (discussed in detail below). A validation study of the ED01 would have required a prohibitively large, much more expensive study. In contrast it would be feasible to study further the 5% of subjects who DO react at ED05, with lower doses, including the ED01.

We feel it is important to standardise this approach at an international level since the findings in this study have consequences for the food manufacturing industry at a global level. Our plans to initiate this study have recently been supported in a review by a large multidisciplinary European group [7]. This may contribute to improvement of precautionary labelling thresholds to be set for use by regulators and manufacturers to protect the food allergic consumer.

Methods

Recruitment

This is a multi-centre study involving three teaching centres. A total 375 participants will be recruited (125 in each centre) during their follow-up appointments in the Department of Allergy in each respective centre.

Inclusion criteria

Each patient must meet all of the following criteria to be enrolled in this study.

- Age between 1 to 18 years old and
- Demonstrate evidence of peanut allergy as defined by either
 - (a) History of unequivocal exposure (including accidental) and typical acute allergic reaction within the preceding 2 years and positive peanut SPT/sIgE, or
 - (b) Positive oral food challenge with peanut performed within 2 years - either open oral food challenge or DBPCFC (Double-blind, placebo-controlled food challenges)
 - (c) Peanut never ingested, but sensitisation to peanut above the 95% positive predictive value (PPV) for clinical allergy, i.e. peanut serum IgE \geq to 15 kU/L (by CAP FEIA) and/or peanut SPT wheal size \geq to 8 mm within 2 months of the single dose challenge.

Exclusion criteria

Patients meeting any of the following criteria will be excluded from the study.

- Family or child does not consent to participate
- Medically unfit for challenge according to local unit OFC guidelines/protocol (e.g., high fever, unwell with intercurrent illness,
- Any objective sign of an acute allergic reaction
- Oral corticosteroids within 14 days prior to challenge
- Episode of anaphylaxis of any cause in 4 weeks prior to challenge
- Use of antihistamines within 5 days of oral food challenge
- Asthma that is not well controlled as demonstrated by FEV1 < 85% of predicted best.

Food Allergy related Quality of Life

Questionnaires-(FAQLQ)

Validated FAQL questionnaires will be self-administered prior to OFC and 1 month after challenge to assess whether the impact of this novel single dose OFC protocol is similar to that of "routine" diagnostic OFC, (Figure 2) (Additional files 1, 2 and 3).

Non-Responder Questionnaire (NRQ)

We aim to administer a non-responder questionnaire (NRQ): a set of questions intended to permit comparison of basic demographic and clinical allergy data in those choosing not to participate and in study participants (Additional file 4). The NRQ that we have developed is similar to the NRQ that was used by Osborne et al. (2010) [8].

Single dose Oral Food Challenge (OFC)

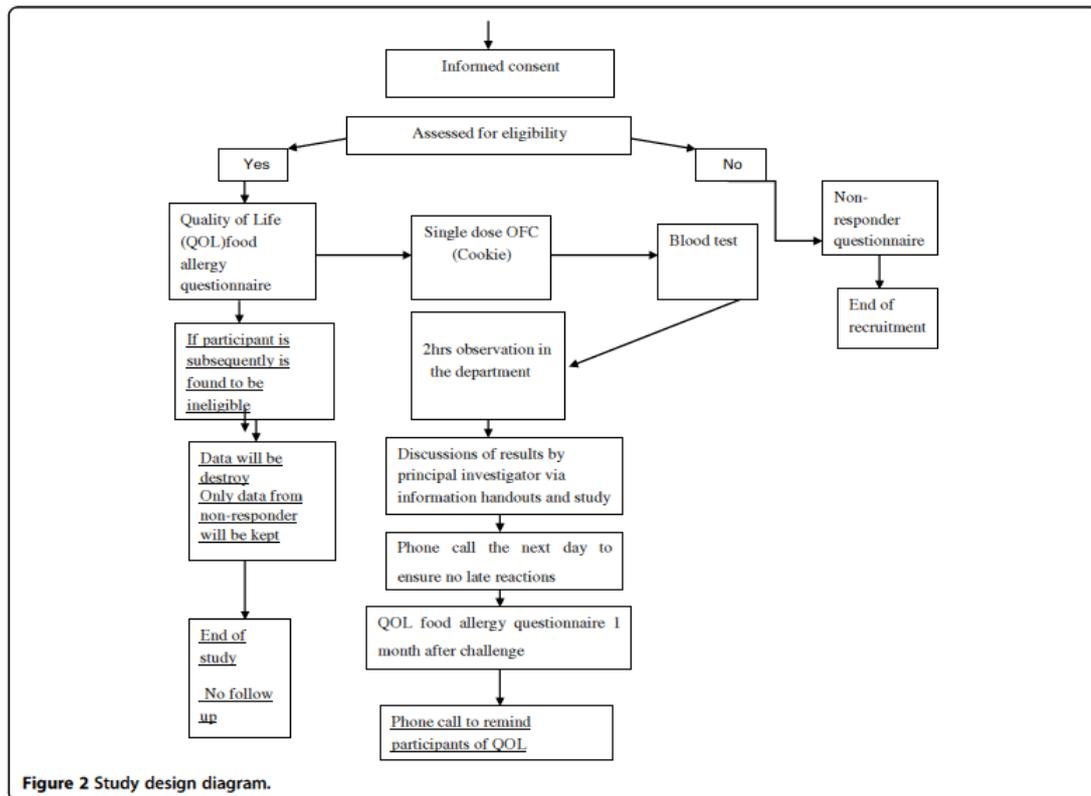
A standard OFC administers multiple doses over 45–120 minutes depending on the challenge protocol. We will give a single dose of peanut, taken in isolation, at the level of the predicted ED05 (6 mg whole peanut = 1.5 mg peanut protein) in the form of a cookie consisting of granulated sugar, brown sugar, all-purpose wheat flour, vegetable shortening, salt and baking soda. Peanut flour will be added at a level that represents 6 mg whole peanut equivalent to 1/100th of whole peanut. For subjects allergic to other cookie ingredients e.g. wheat, the peanut dose will be administered in a food known to be tolerated. The challenge materials are shelf-stable and are manufactured at The University of Nebraska and then distributed to participating clinic centres.

Criteria for a positive OFC result

Only objective criteria will be used in the validation of the ED05, since that dose was predicted on the basis of challenge-associated objective responses only. Objective criteria are outlined by Sampson et al. in the PRACTALL criteria [9] and have been validated in the Healthnuts study [10]. These criteria include urticaria, perioral or periorbital angioedema, vomiting, diarrhoea, respiratory or cardiovascular compromise (including anaphylaxis) and rhinoconjunctivitis. All objective signs will be quantitated in number, site and duration of presence. Participants in OFC often expect severe outcomes following ingestion; this may manifest as subjective symptoms. Subjective symptoms will be recorded but not used in the analysis of the reactions to validate the derived ED05 because the ED05 was developed only on the basis of objective reactions. Subjective symptoms to be recorded include: Headache, dizziness, bloating, abdominal pain, cramps, muscle aches, aching joints, anxiety, tension, agitation [11,12].

The prior agreed objective criteria for a positive OFC result are any objective signs occurring within 2 hours of ingestion. All objective signs will be recorded:

- 3 or more concurrent noncontact urticaria persisting for at least 5 minutes;
- perioral or periorbital angioedema;
- rhinoconjunctivitis
- diarrhoea
- vomiting (excluding gag reflex); or



- evidence of circulatory or respiratory compromise (anaphylaxis eg, persistent cough, wheeze, change in voice, stridor, difficulty breathing, and collapse) [10].

Blood test

A blood sample (10 ml) will be taken for peanut component analysis and quantitative peanut-specific IgE fluoroenzyme immunoassays 20 minutes after OFC.

Sample size estimation

The population proportion of peanut allergic children who react to the nominal ED₀₅ dose of peanut will be estimated, separately for each of the three participating centres, as the corresponding observed proportion of participants. If, based on these three proportions, there is strong evidence against the null hypothesis that the proportion reacting is the same in all three centres then centre-specific estimates will be reported, otherwise the proportion aggregated over all three centres will serve as a single centre-independent estimate. 95% confidence intervals for these population proportions will be calculated using the properties of the binomial distribution. Example of 95% confidence intervals for sample sizes 70,

100, 150, 200 and 375 if the estimated prevalence is equal to the nominal value of 5%, are displayed in Table 1. A sample size of 150 corresponds to a lower confidence limit of 2.3% and an upper confidence limit of 10%. While this implies that the population proportion may be as little as half or as much as double the observed proportion, this calculation is conservative since it uses the sample size expected in a single centre, not from the three centres

Table 1 Projected 95% confidence intervals for the prevalence of clinical reactivity in peanut allergic children and adults receiving the ED₀₅ dose (6 mg of whole peanut = 1.5 mg of peanut protein) for sample sizes ranging from 70 to 200

Sample size (of peanut allergic individuals)	Value of target prevalence (5% for the ED ₀₅)	Projected 95% confidence interval
70	5%	0.9% - 12%
100	5%	1.6% - 11%
150	5%	2.3% - 10%
200	5%	2.4% - 9%
375	5%	3.1% - 7.8%

combined, so it is sufficiently accurate to rule out gross incompatibility between the nominal and observed proportion of participants reacting.

Summary statistics will be used to compare the features of participants and non-participants, and of ED05-reactors and non-reactors. Variables to be examined will include clinical severity of previous reactions, age, sex, SPT wheal size and peanut component-specific IgE levels. Multivariable logistic regression analyses will be used to identify combinations of these features that identify the low-dose reactors.

Ethics/Patient safety

This Study has been approved by Cork University Hospital Research Ethics Committee (ECM 4 g), Royal Children's Hospital Human Research Ethics Committee (HRECApp 32166A), and Massachusetts General Hospital Research Ethics Committee (2012P002475). Written, informed parental and adolescent consent and assent from younger children will be recorded before participation in the PATS challenge. An External Safety Monitor has been appointed who is an experienced allergist, not otherwise involved in this study or related studies in the study centres.

Discussion

The estimation of the threshold dose for allergic reaction to peanut in peanut allergic subjects has potential value for public health measures. The use of statistical dose-distribution modelling based upon the results of low-dose clinical challenges of peanut-allergic individuals has been viewed as a strong approach to estimation of the population threshold for peanut [13,14].

However, the clinical determination of individual thresholds is based upon graded incrementally increasing challenge doses administered at convenient time intervals, sometimes as short as 15–20 minutes between doses. The individual threshold doses are frequently reported as cumulative doses because it is impossible to claim that each dose is fully assimilated before administration of the next dose [15].

Allen et al. (2013) used this approach to estimate a population threshold for the peanut-allergic population based upon challenges of 750 individuals. The ED05 from the log normal dose-distribution was 6 mg of whole peanut or 1.5 mg of peanut protein. Since cumulative doses were used in the evaluation of individual challenges and subsequent statistical dose-distribution modelling, it is important to validate the peanut ED05 using a single-dose approach. Peanut is the best-studied food allergen in terms of low dose OFC to date. This novel PATS approach could be adapted for other major food allergens, if this proposed clinical study supports the statistically determined ED05 based upon population dose-distribution modelling [1].

The plan to approach all peanut allergic subjects in 3 distinct geographical regions the varied or permissive entry criteria and the analysis of the non-participants will address the most common criticism of OFC studies: how representative of the general peanut allergic population are the subjects who volunteered? Peanut allergic subjects who have food challenges are highly selected and they may not represent the whole spectrum of reactivity to peanut in peanut allergic subjects [16].

The strict requirement for only objective signs being used to determine a case is important, because subjective reactions are known to resolve during a routine OFC that is continued until objective signs are recorded [10,17].

Peanut allergic patients are usually advised to avoid foods that are labelled as "may contain" peanut. A recent study by Madsen et al. (2012) has showed that it is understood and accepted by clinicians, patients and food producers that zero risk is not a realistic or attainable option [18]. However clinical risk communications that are not specific may increase anxiety and risk taking behaviours without increasing awareness, confidence or safety [7].

Currently there is no standard approach being used by all manufacturers in relation to precautionary labelling. This may be due, in part, to the lack of agreement among the scientific community regarding clinically safe threshold levels. If this current study validates the ED05 this will aid the scientific and medical communities and also the manufacturing industry in the use of quantitative precautionary labelling, backed with sound scientific evidence for the establishment of safe threshold levels for 95% of the peanut allergic community.

The PATS study offers a new clinical paradigm and methodology with regards to assessing clinical risk; this current study may potentially define the 5% of patients who are most highly sensitive. Validated questionnaires assessing FAQL have shown patients gain nearly as much from a "failed" OFC as they do from a "passed" OFC, probably due to decreased uncertainty about the next and future reactions [19] and we hypothesise that individual families may also show such an improvement after a PATS single dose challenge. This tangible impact could promote adoption of PATS single dose peanut challenges in units not currently performing diagnostic OFC. If this proposed clinical study supports the statistically determined ED05 based upon population dose-distribution modelling of peanut, it may show promise for clinical validation of other allergenic food sources where sufficient threshold data is available to model the population dose-distribution. Eventually a single-dose diagnostic OFC using other food allergens may be adopted as well.

Clinicians may be able to use PATS single dose OFCs as they are easier to perform than routine diagnostic OFC or DBPCFC and they could contribute to the complex analysis of risk that clinicians currently make in a

heuristic fashion that varies between practitioners. Currently clinicians make value judgements about whether they believe a child to be exquisitely sensitive to a food or not and therefore what to advise with regards to avoiding trace amounts of allergen in food (i.e. foods with precautionary labelling).

The single dose protocol does not replace current clinical food challenges which are for the diagnosis of food allergy but would provide extra clinical information of patients' level of risk and could help inform consumer choices and physician advice to patients regarding precautionary labelling [20,21]. This project may offer a practical way to discern whether allergic patients can safely ingest foods with labels such as "may contain traces", although this outcome would require collaboration with the food industry and more uniform adoption of criteria for use of precautionary labels as proposed in the Australian VITAL strategy.

Conclusion

The PATS single dose OFC, based upon the statistical dose-distribution analysis of past challenge trials, promises an efficient approach to identify the most highly sensitive patients within any given food-allergic population. The peanut protocol described herein will evaluate the practicality of this approach and allow assessment of its safety. The validation of the ED05 originally statistically determined from the dose-distribution analysis would be a major benefit of the study as it would serve to inform governments in the application of a more transparent and sensible approach in the use of precautionary labelling. It will also aid public health agencies in the establishment of approaches to allergen management that will protect the vast majority of food-allergic consumers/patients.

Additional files

Additional file 1: Food Allergy Quality of Life Questionnaire –Parent Form (0–12 years).

Additional file 2: Food Allergy Quality of Life Questionnaire–Child Form (8–12 years).

Additional file 3: Food Allergy Quality of Life Questionnaire–Teenager Form (13–18 years).

Additional file 4: Peanut single dose study, non-participant questionnaire.

Competing interests

GZ declares that he has no competing interests. JH has received speaker honoraria and travel support from Stallergenes, Nutricia, Mead Johnson, Pfizer, Astra Zeneca, and MSD. He has received research funding from Danone and Stallergenes. KA has received speaker's honorarium from Pfizer, Abbott and Danone. ST declares that he has no competing interests. WS, JB, LG, MM, MT, JN, ADG declares that he has no competing interests.

Authors' contributions

GZ made substantial contribution to the conception, design and revising the manuscript. KA is local clinical PI on the study and made substantial

contributions to the development of the study design and protocol made substantial contribution to the conception and design of the manuscript. ST devised the original research concept with JH, JB and others and has revised the manuscript critically for important intellectual content. WS has revised the manuscript critically for important intellectual content. JB devised the original research concept with JH, ST and others and has revised the manuscript critically for important intellectual content. MT has contributed to refinement of the study protocol and review of manuscript LG reviewed the epidemiological study design, proposed the statistical analysis plan and contributed to the writing and revision of the paper. MM has contributed to the revision of the paper. JN has contributed to the drafting of the manuscript. ADG contributed to study design and has contributed in drafting and revising the manuscript. JH is lead clinical PI on the study and developed the original research concept with ST. He made substantial intellectual contribution to the manuscript, has been involved in drafting and giving final approval of the version to be published. All authors read and approved the final manuscript.

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Chapter 10: Discussion, conclusion and future research direction

From my own experience in dealing with children who are non-tolerant to food allergens, I have been exposed to the extremely difficult task of shopping for children on restricted diets. I have often wondered to myself: are these statements really helping my family and me? Also, what is the level of risk if I choose to consume these products that contain precautionary statements?

To answer these questions, my first paper set out to investigate the prevalence of precautionary statements within a supermarket setting. My results showed that more than half (65%) of processed foods had a precautionary statement for one or more allergens. The strengths of this study are the large number of food products examined and the detailed assessment of precautionary labelling for both the allergen/s listed and the type of precautionary statements used. Although the selection of a single supermarket for this assessment may be considered a methodological limitation, I chose this as there are two main supermarket chains (a duopoly), which accounts for approximately 85% of supermarkets in Australia. Furthermore, my assessment of food labels was not restricted to a single brand but all brands were examined with an equal proportion of food brands assessed.

Previously, the prevalence of mandatory precautionary statements within a supermarket setting was not known in Australia. In addition, no formal study had examined the uptake of the VITAL process. Future research could investigate the prevalence of precautionary statements on frozen foods such as ice-creams as this has not yet been investigated. Also, since this paper has been published, an enormous amount of effort

has been invested by the Allergen Bureau in promoting VITAL both locally and internationally. They have also updated their process to VITAL2.0. Future research could investigate the prevalence of the VITAL “may be present” statements versus other forms of precautionary statements to examine whether manufacturers now have a preference to use VITAL due to the increase in publicity around the VITAL process.

There is some evidence in European studies to suggest that consumers are complacent when it comes to taking notice of precautionary food labels. However, food allergic consumers’ perceptions of precautionary labelling had not been investigated in Australia before; therefore consumer behaviour was unknown in the Australian setting. I chose to examine the behaviours of the food allergic consumers when shopping for themselves or for their food allergic children.

My second paper investigated consumer perceptions of precautionary labelling in families with food allergy and anaphylaxis in Australia. I designed a questionnaire-based study of a consecutive series of parents of children attending the Department of Allergy at The Royal Children’s Hospital, Melbourne. My objective was to understand consumer behaviours and perceptions regarding precautionary labelling in those with or without a history of anaphylaxis.

My results showed that 84% of participants considered precautionary labels not useful and that the majority of participants (>90%) felt that these labels only protected the manufacturer from litigation. I stratified the data by creating two groups: those with a history of anaphylaxis and those with a history of mild-to-moderate IgE mediated reactions. What was surprising was that there was no difference in consumers’

behaviours as to whether or not they had the history of anaphylaxis. This finding was very interesting as I had earlier presumed that parents of children with severe reactions (such as a history of anaphylaxis) would be more cautious when shopping, but this was not the case.

Some of the strengths of the study are that all participants were recruited in a consecutive matter and that the response rate was high (93%). This limited any potential for sampling bias. One limitation of the study is that I relied on patient reports of reactions. Only after completing this survey did I realise that it would have produced more accurate results if I had documented histories of reactions and confirmed these. This, however, would have meant checking patient records or asking the treating doctor for verification of the participant's history of reaction. Future research could access participants' clinical data and validate responses through clinical notes to confirm a previous history of anaphylaxis or mild-to-moderate IgE mediated reactions. In addition, this study provided no education to participants regarding the VITAL process. Future studies could educate participants by outlining the differences between the "may be present statement" versus other precautionary statements and then examine whether participants were willing to adhere to this statement without their doctor's endorsement.

Given the fact that most of the allergic consumers were ignoring precautionary labelling irrespective of what their history of reactions was, I wanted to examine the risk to consumers who chose to ignore precautionary labelling in the Australian setting where approximately 2 supermarkets are responsible for the major markets.

My third paper investigated the level of cross contamination of peanut, hazelnut, milk, egg, soy, and lupin in 135 processed foods with precautionary statements by visiting three different Australian supermarkets (Woolworths, Coles and Aldi). I examined five categories of high-risk foods defined by the high level of precautionary labelling most likely to be contaminated. These included chocolates, breakfast cereals, muesli bars, savoury biscuits and sweet biscuits. The samples underwent analysis by FACTA with the use of ELISA kits that were donated by the University of Nebraska.

My results showed that of the 128 samples, only nine (7.0%) with precautionary labelling had detectable levels of peanut. Of all other samples that had precautionary labelling for hazelnut, milk, egg, soy or lupin, none were found to have any detectable level of those allergens. These results showed that consumers were not really exposing themselves to a substantial risk by ingesting foods with precautionary labelling as there were no allergens in the foods that I tested with the exception of peanut. These results led me to believe that consumers' actions were justified when they chose to ignore precautionary statements as the level of risk was low.

The strengths of the study are that I analysed food products from three different supermarkets that represent both the Australian and European industry. Also, I tested three samples of each product. Each sample came from a product purchased from a different supermarket within each chain, with each purchase taking place at a supermarket in a different location. Some of the limitations include a reasonably small selection of goods being purchased for analysis of cross contamination and that I could not exclude the fact that different batches of the same products may have contained different levels of allergens. However other studies that have investigated cross

contamination in processed foods have only done so for a limited number of allergens; none have investigated a whole range of allergens in which labelling is mandatory as in this current study.

Further studies could investigate a larger selection of processed foods as my study was limited to a small selection of goods. Also it would be of interest to investigate cross contamination for all tree nuts as my study only investigated hazelnut. Particular attention to cross contamination involving cashew would also be of much interest as cashew is one of the most prevalent tree nuts to which children are sensitised. It was my intention to test foods for cross contamination with cashew, however at the time of my study there were no commercial kits available.

The results of the paper show that peanut was the only allergen that had detectable traces of allergen. These levels were very low and it cannot be certain that a child with peanut allergy would have a reaction to this amount. It is known that children who have food allergy have threshold levels and that as long as their particular level is not exceeded then there should be no reaction. But was the amount that I had found higher or lower than this threshold level?

For my fourth paper I conducted a detailed search of the literature to examine what other authors had been investigating regarding thresholds levels for the peanut allergic community. My results showed that internationally, food allergic consumers were disregarding precautionary labelling and that cross contamination was a common cause of accidental exposure to food allergens. In fact, all of the studies that I reviewed spoke of detectable traces of allergens, but once again these amounts were very low and

similar to my results for peanut. The investigation also revealed other authors' work that had established estimates of eliciting doses (ED) that may have caused mild objective allergic reactions in 5% of the allergic community.

The established ED05 is 6 mg of whole peanut which equals 1.5 mg of peanut protein. This was of immediate interest to me as I was able to determine that of the published literature that I reviewed and from my recent results, the detectable levels that have been observed were lower than the predicted ED05. I could then postulate that the levels detected would be unlikely to cause severe allergic reactions.

A limitation of the ED05 is that the data has been estimated with children undergoing OFC which relies on incremental doses of the allergen at fixed time intervals, therefore it cannot be certain to which dose the child is reacting. Future studies could examine the safety and acceptability of offering a single dose equivalent to the ED05 to help to validate the current estimate of ED05.

My fifth and last paper outlines the methods of such a study and explains that it is a multi-centre study involving three teaching centres (University Hospital UCC Cork, Ireland, Royal Children's Hospital Melbourne, Australia and General Hospital, Food Allergies Centre, Massachusetts, Boston, U.S.A.). A total of 375 participants were recruited during their follow-up appointments in the Department of Allergy in each respective centre. The aim was to assess the precision of the predicted ED05 using a single dose (6mg peanut = 1.5mg of peanut protein) in the form of a cookie. A strength of the study is that every person with peanut allergy presenting to their respective centres will systematically be offered a low dose peanut challenge. A limitation is that

this current study's aim is to establish threshold levels for peanut only. If this study is successful in validating the ED05 for peanut, then further studies could also validate threshold levels for other allergens.

The validation of threshold levels for all major allergens would have a dramatic impact on the manufacturer and the food allergic consumer alike. The manufacturing industry would have standardised protocol for precautionary labelling that could be implemented internationally and this would aid in restoring consumer confidence in the labelling system. In addition, this process requires that any foods that fall into a bracket lower than the validated threshold levels should not contain a precautionary statement. This would potentially make more than half of processed foods within the supermarket more accessible rather than having the ambiguous form of labelling that is now present.

My research has shown that food allergic consumers' attitudes towards precautionary labelling appear to be complacent and that this is irrespective of a history of anaphylaxis. My work has also shown that precautionary labelling is prevalent, ambiguous and often ignored; in fact contrary to medical assumptions, consumers may not be undertaking substantial risk in their ingestion of these products. Policies that promote the more effective use of precautionary statements are urgently required.

Further studies could investigate the benefits of a national reporting system to catalogue and investigate adverse reactions to foods with precautionary labelling as this would enable assessment of whether or not allergic consumer behaviour in Australia is appropriate.

In addition, the level of risk to food allergic consumers (if any) could be investigated by observing food allergic consumers over a one year period. The study could recruit participants who have a doctor diagnosis of food allergy with a past history of anaphylaxis and who choose to ignore these statements. A control group that is milder in allergic history and that observes precautionary statements could also be useful. The study could document the severity of reaction with these two groups in the Australian setting where >70% of consumers choose to ignore precautionary statements. Lastly, in our multi-ethnic population, there may be a large number of parents who do not speak English. It would be of interest to investigate how these families with children who have food allergy cope in relation to precautionary statements. Such studies as these mentioned would inform food manufacturers and regulatory bodies of the usefulness of precautionary statements on processed foods.

In conclusion, my work clearly demonstrates that precautionary labelling is prevalent and is often ignored by the food allergic consumer. It also shows that the current state of play of precautionary labelling is not in the best interests of the food allergic community. The lack of legislation and agreement of threshold levels continues to undermine the credibility of precautionary labelling.

In my opinion, the only way to come to a positive outcome to this matter may be to consider adopting protocols as done by the governments of Japan and Switzerland. New practices such as the VITAL 2.0 process (if legislated) will also help to validate food labels and restore consumer confidence in these labels.

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Appendix 1: Consumer perceptions of precautionary labelling in families with food allergy and anaphylaxis in Australia questionnaire

Participants questioner

About you

Date of birth: / / Age: Gender: Male Female

Your postcode:

About your child

Date of birth: / / Age: Gender: Male Female

1. Has your child been doctor diagnosed with food allergy? Yes No

(If yes, please ✓ all that apply)

- Peanut Tree nut Egg Milk Fish Sesame Soy
 Wheat Lupin Crustaceans Other

Please specify: _____

3. Has your child eaten any of the above food?

Yes No Not sure

4.If your child has not eaten the food, was the diagnosis made by:

- a) Skin test only
b) Reaction following contact with the food (WITHOUT having eaten the food)
c) Other

Please specify _____

5. Does your child have any of the following conditions?

(If yes, please ✓ all that apply)

6. During the MOST SEVERE allergic reaction to a food product, did your child have any of the following symptoms? (Tick all that apply)

- | | | | |
|--|------------------------------|-----------------------------|-----------------------------------|
| Swelling of the eyes/lips or face | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |
| Hives (<i>also called urticaria; itchy rash like mosquito bites</i>) | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |
| Vomiting | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |
| Diarrhoea | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |
| Abdominal pain | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |
| Pale or loss of energy | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |
| Anaphylaxis (<i>itchy throat or mouth, throat tightness or choking, coughing, wheezing or trouble breathing, collapse</i>) | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |

7. Did your child use any of the following during that MOST SEVERE allergic reaction? (Tick all that apply)

- | | | | |
|---|------------------------------|-----------------------------|-----------------------------------|
| Treatment at emergency department or hospitalization | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |
| Antihistamine (<i>e.g. Zyrtec, phenergan</i>) | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |
| Adrenaline (eg Epipen) | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |
| Steroids/ Prednisolone | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |
| Asthma medicines (<i>e.g. inhalers, or face mask</i>) | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Not sure |

There is currently varying opinion amongst doctors on whether families of children with allergy should avoid foods with precautionary labelling or whether it is safe to ignore this type of labelling. We are trying to gather information on what you NORMALLY do in your daily life with regards to managing your child with food allergy. We don't want you to respond with answers that your allergist or doctor has suggested that you do – we would like you to tell us what you actually do.

8. If your child is allergic to e.g. peanuts do you avoid having those products in the house?

Yes No Not sure

9. When you buy a food do you check for allergens in the ingredient list, the precautionary labelling list, both or neither

Ingredient only Precautionary only Both Neither

If neither please specify why _____

10. Would you give your child a food if the food they were allergic to was listed in the precautionary labelling section? Yes No Not sure

11. Would you give your child a food that they were allergic to if it was listed in one or more of the following categories? (Please tick for every category):

I would give a food that had labelling

May contain Yes No Not sure

May contain traces of Yes No Not sure

Made on the same production line Yes No Not sure

Manufactured in a facility that also processes	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure
Manufactured on shared equipment with products containing	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure
Manufactured on a line that processes	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure
Packaged in a facility that also packages products containing	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure
Processed on equipment that makes products containing	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure
Produced in a plant which manufactures products containing	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure
Made on the same equipment	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure
Made in the same factory	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure
Made in the same premises	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure
May be present	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not sure

12. What do you understand by the statement “May contain traces” to mean? Please respond to all statements

	True	Probably True	Possibly True	Possibly False	Probably False	False
The food IS PRESENT in the product due to manufacturing techniques	<input type="checkbox"/>					
The food MIGHT be present in the product due to manufacturing techniques	<input type="checkbox"/>					
There are only small amounts of the food present, therefore it is SAFE to eat	<input type="checkbox"/>					
There are small amounts of the food present, therefore it is NOT SAFE to eat	<input type="checkbox"/>					
The risk of cross contamination is LOW , but may be possible	<input type="checkbox"/>					
This statement only protects the manufacturer from litigation	<input type="checkbox"/>					
I do not find this statement useful, as I don't know if it is safe to eat	<input type="checkbox"/>					

13. What do you understand by the statement “Made on the same production line” to mean? Please answer all statements

	True	Probably True	Possibly True	Possibly False	Probably False	False
The food IS PRESENT in the product due to manufacturing techniques	<input type="checkbox"/>					
The food MIGHT be present in the product due to manufacturing techniques	<input type="checkbox"/>					
There are only small amounts of the food present, therefore it is SAFE to eat	<input type="checkbox"/>					
There are small amounts of the food present, therefore it is NOT SAFE to eat	<input type="checkbox"/>					
The risk of cross contamination is LOW , but may be possible	<input type="checkbox"/>					
This statement only protects the manufacturer from litigation	<input type="checkbox"/>					
I do not find this statement useful, as I don't know if it is safe to eat	<input type="checkbox"/>					

14. What do you understand by the statement “Made on the same equipment” to mean? Please answer all statements

	True	Probably True	Possibly True	Possibly False	Probably False	False
The food IS PRESENT in the product due to manufacturing techniques	<input type="checkbox"/>					
The food MIGHT be present in the product due to manufacturing techniques	<input type="checkbox"/>					
There are only small amounts of the food present, therefore it is SAFE to eat	<input type="checkbox"/>					
There are small amounts of the food present, therefore it is NOT SAFE to eat	<input type="checkbox"/>					
The risk of cross contamination is LOW , but may be possible	<input type="checkbox"/>					
This statement only protects the manufacturer from litigation	<input type="checkbox"/>					
I do not find this statement useful, as I don't know if it is safe to eat	<input type="checkbox"/>					

15. What do you understand by the statement “Made in the same factory” to mean? Please answer all statements

	True	Probably True	Possibly True	Possibly False	Probably False	False
The food IS PRESENT in the product due to manufacturing techniques	<input type="checkbox"/>					
The food MIGHT be present in the product due to manufacturing techniques	<input type="checkbox"/>					
There are only small amounts of the food present, therefore it is SAFE to eat	<input type="checkbox"/>					
There are small amounts of the food present, therefore it is NOT SAFE to eat	<input type="checkbox"/>					
The risk of cross contamination is LOW , but may be possible	<input type="checkbox"/>					
This statement only protects the manufacturer from litigation	<input type="checkbox"/>					
I do not find this statement useful, as I don't know if it is safe to eat	<input type="checkbox"/>					

16. What do you understand by the statement “Made in the same premises” to mean? Please answer all statements

	True	Probably True	Possibly True	Possibly False	Probably False	False
The food IS PRESENT in the product due to manufacturing techniques	<input type="checkbox"/>					
The food MIGHT be present in the product due to manufacturing techniques	<input type="checkbox"/>					
There are only small amounts of the food present, therefore it is SAFE to eat	<input type="checkbox"/>					
There are small amounts of the food present, therefore it is NOT SAFE to eat	<input type="checkbox"/>					
The risk of cross contamination is LOW , but may be possible	<input type="checkbox"/>					
This statement only protects the manufacturer from litigation	<input type="checkbox"/>					
I do not find this statement useful, as I don't know if it is safe to eat	<input type="checkbox"/>					

17. What do you understand by the statement “May be present” to mean? Please answer all statements

	True	Probably True	Possibly True	Possibly False	Probably False	False
The food IS PRESENT in the product due to manufacturing techniques	<input type="checkbox"/>					
The food MIGHT be present in the product due to manufacturing techniques	<input type="checkbox"/>					
There are only small amounts of the food present, therefore it is SAFE to eat	<input type="checkbox"/>					
There are small amounts of the food present, therefore it is NOT SAFE to eat	<input type="checkbox"/>					
The risk of cross contamination is LOW , but may be possible	<input type="checkbox"/>					
This statement only protects the manufacturer from litigation	<input type="checkbox"/>					
I do not find this statement useful, as I don't know if it is safe to eat	<input type="checkbox"/>					

18. Do you agree or disagree with the following statement?

Generally speaking, it is easy to understand and use the ingredient list information on food labels

- Agree Disagree

19. How often do you look at precautionary food labels?

- Only when I buy a product for the first time
 Only occasionally when I buy a product
 Most of the times I buy a product
 Every time I buy a product

20. Do you feel that you can trust the information on precautionary food labels?

- I completely trust what the label says
 I'm pretty sure that I can trust what the label says
 I do not trust what the label says
 I'm not at all sure whether to trust the labels or not

21. If you are unsure about what is written in the precautionary food labels, which of the following do you do?

- Do not allow my child to use/eat the food
 Ring the manufacturer and ask
 Ring my child's dietician or doctor
 Ring a support group
 Allow my child to try eating a small amount
 Try rubbing some inside my child's lip and wait to see what happens
 Allow my child to eat the food anyway

22. Do you feel that there should be better government regulations imposed upon manufacturers of food products in the way they use precautionary labelling?

- Yes No Not sure

If yes, please state what type of controls **YOU** would like to see:

23. This question is about making changes to precautionary labelling. We have developed four different methods of labelling, and wish to identify which one (or all) best suits you.

(a) The “may be present” statement. If you were assured that this statement represented a LOW level of cross contamination from a food allergen, would you:

Find this statement useful? Yes No Not sure

Consume foods with this statement? Yes No Not sure

Consume foods with this statement only if your doctor or allergy specialist said it was safe to do so? Yes No Not sure

(b) If you were assured that this symbol represented a VERY LOW level of cross contamination from a food allergen



Would you:

Find this symbol useful? Yes No Not sure

Consume foods with this symbol? Yes No Not sure

Consume foods with this statement only if your doctor or allergy specialist said it was safe to do so? Yes No Not sure

(c) If there was an independent toll free number listed on all food products that you could call to gain more information regarding the product's ingredients

Would you:

Find this service useful? Yes No Not sure

Consume foods after using this service? Yes No Not sure

Consume foods with this statement only if your doctor or allergy specialist said it was safe to do so? Yes No Not sure

If you have food allergies and are concerned about the ingredients of this product please call
1800 allergies
180025537437

(d) If there was a mobile phone application in which you could scan the barcode of a food product and instantly receive more information regarding the ingredients



Would you:

Find this application useful? Yes No Not sure

Consume foods after using this application? Yes No Not sure

Consume foods with this statement only if your doctor or allergy specialist said it was safe to do so? Yes No Not sure

Thank you for completing our survey. Your contribution to our research is valuable and we appreciate your help.

Non-responder questionnaire

If you are unwilling or unable to participate in this study we would really appreciate if you would tell us why. This information will help us to understand why some people may not wish to participate in this study and will help to ensure our research is undertaken in the most ethical and effective way. You don't have to answer these questions but we would appreciate it if you would.

1) Why have you chosen not to participate in the study?

Too busy

Not interested

Do not care about the issue

Not the right time

Non-English speaking background

Not relevant to me

Other
Please specify

What is your postcode? -----