Development of VITAL Allergen Actions Levels Grid

Explanatory notes

(Prepared by

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INTRODUCTION

The Australia New Zealand Food Standards Code Standard 1.2.3 - Mandatory Warning and Advisory Statements and Declarations requires the mandatory declaration of the presence in a food of any of a list of allergens[1] when these are present as an ingredient; an ingredient of a compound ingredient; a food additive or component of a food additive; a processing aid or component of a processing aid.

In addition to named allergens present in a food due to direct, intentional addition as a component of one of these vehicles, allergens may also be present, under conditions of Good Manufacturing Practice (GMP), due to cross contact with other products, in which they are present, that have been produced in the same establishment and/or on the same equipment. The VITAL Allergen Action Level Grid ("Vital Grid") and associated procedures have been developed to provide a systematic risk based approach for manufacturers to determine whether allergens in food due to incidental cross contact should be labelled and, if so, whether this labelling should be as potentially present or actually present (ie identified as an ingredient). It is not intended that the VITAL Grid will be used when a manufacturer has intentionally added an allergen as a component of one of the food vehicles listed above.

CLINICAL STUDIES

A range of clinical studies which have been undertaken to investigate responses to allergens in food are available. The studies range from single blind to double blind trials and cover a range of methodologies (1-6). In the majority of cases the studies have been undertaken on individuals already diagnosed with allergies, to observe the pattern of onset of symptoms rather than to establish no effect thresholds (NOAELs).

In the majority of cases, subjects are given gradually increasing doses of food containing the allergenic material (eg peanut butter, fish, egg) over a period of time. Allergenic responses are recorded. These responses may be categorised as subjective and objective responses. Subjective responses can include numbness or pruritis at the site of contact or general uneasiness and rely on reporting by the subject under investigation. Objectives symptoms are independently observable by a third party and include, but are not limited to, flushed skin, hives, or swelling of the lips and face. The symptoms may be mild and short-lived or they may, occasionally, be more severe, involving the respiratory and cardiovascular systems.

A general concern about the studies is that severe allergy sufferers may have been

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1 Cereals containing gluten and their products, namely, wheat, rye, barley, oats and spelt and their hybridised strains other than where these substances are present in beer and spirits standardised in Standards 2.7.2 and 2.7.5 respectively
Crustacea and their products
Egg and egg products
Fish and fish products
Milk and milk products
Peanuts and soybeans, and their products
Added Sulphites in concentrations of 10 mg/kg or more
Tree nuts and sesame seeds and their products

reluctant to participate and/or may have been excluded for ethical reasons and that the studies are therefore skewed to mildly affected subjects. On the other hand, most reported studies have been conducted at specialist allergy referral clinics and will therefore include mainly patients whose allergy is difficult to control, potentially skewing the tested population in the opposite direction.

The amount of allergenic protein is generally expressed as total protein derived from the allergenic material and is frequently determined from standard tables rather than analysis of the actual food tested (eg: peanut butter has been assumed by researchers to contain 50% peanut protein). Because many of the studies do not demonstrate no effect levels (ie at least one subject reacts at the lowest dose tested), the results are commonly presented as LOAELS (Lowest Observed Adverse Effect Levels). The LOAELS from the available data have been summarised by the US FDA Threshold Working Group (7) as follows:

Table 1 - Summary of Published LOAELs for Food Allergens

Food	**Range of LOAEL (mg protein)**
Egg	0.13 - 1.0
Peanut	0.25 - 10
Milk	0.36 - 3.6
Tree Nuts	0.02 - 7.5
Soy	88 - 522
Fish	1 - 100

Gluten
Thresholds for gluten have been based on reported gastrointestinal effects related to coeliac disease. A threshold for coeliac sensitivity has been reported in the range 20 - 100 ppm gluten (7). This range has been used in the determination of action levels for labelling.

Crustacea
The project team determined that Crustacea should be included in the table using the levels for peanuts.

Sesame
The project team determined that sesame should be included in the table using the levels for peanuts.

Uncertainties

Uncertainties arising from the use of the current published data include:

- Adequacy of clinical trial data. In particular, the reporting of LOAELs rather than NOAELs;
- Intra-individual differences within the human population;
  (Toxicologist typically apply a 10-fold uncertainty factor to account for the variability within a species however this has not been validated in the case of allergic responses. In the present situation this may be considered to be very conservative since, the challenge studies provide information on the likely intra-individual variability of up to 90-95% of the allergic population, depending on the number of people tested. The uncertainty factor incorporated into the action level only addresses the variability of the remaining 5-10%.);
- Sensitivity of the test population compared to the population as a whole;
  Do the studies capture the most sensitive individuals? Can this be addressed by the use of an intra-species safety factor;
- The reporting of total protein from a food rather than the level of specific allergenic proteins; and
- Variability in experimental conditions and food matrices.

THE VITAL GRID

In summary the VITAL Action Levels indicated are:

- **Action Level 1 – Green Zone** - precautionary cross contact statement is not required for the relevant allergen under evaluation.

- **Action Level 2** – **Yellow Zone -** precautionary cross contact statement is required for the relevant allergen using the standard VITAL statement.

- **Action Level 3** – **Red Zone –** significant levels of the allergen are likely to be present. Labelling of the relevant allergen as present is approrpiate.

The VITAL cross contact statement is "May be present: XXX"

The lowest LOAELs for total allergen protein reported from clinical trials were taken in the first instance as indicative of an appropriate amount of allergen protein to trigger allergen labelling following incidental cross contact. These trigger amounts were subsequently adjusted (mostly reduced) to ensure the resulting action levels were achievable whilst reflecting wider industry and community expectations. The trigger level for tree nuts was increased from the LOAEL reported by the FDA (0.02 mg protein) to a level consistent with peanuts and egg (0.1 mg) to ensure the level was measurable in food. In the case of soy, the project team expressed concern about the apparently high LOAELs reported by the FDA (see above) and chose to significantly lower the trigger amount (0.5 mg) used as the basis for determining action levels.

The transition points between the Action Levels have been expressed in terms of a concentration of protein (expressed in ppm) that reflects the amount of total protein (mg) from the allergenic food that must be present in a reference quantity of food for a consumer to receive the selected trigger amount allergen (Table 2). A food portion of 5gm has been taken as the reference quantity for calculation of the grid, equivalent to one Australian teaspoonful of food. The rationale for selecting this quantity of food is that the resulting action level represents a trigger amount (LOAEL, or lower) of allergen, in a small mouthful of food. This is intended to reflect an amount of food after which a moderately sensitive individual might begin to experience subjective reactions.

Since the action levels are derived from an absolute amount of protein, the levels may be customised for larger serving sizes using the following formula:

Customised action level (ppm) = Action level (ppm) x (5/revised serving size (expressed as gm food))

A 10 fold safety factor has then been applied to the derived concentration of allergen in the food to achieve the proposed lower action level. This safety factor is the level normally applied by toxicologists to take account of intra-species variation with a population. It is assumed that exquisitely sensitive individuals will be aware of their status and will not be choosing the complex processed foods for which the VITAL Allergen Action Levels Grid is intended to be applied. Therefore, a second 10 fold safety factor, as proposed in the FDA report on allergens, to take account of ultra sensitive individuals has not been applied.

Action Level 1 - Green Zone

The level of allergen protein in a reference quantity of food is below the lower transition point - no precautionary is labelling required.

Action Level 2 - Yellow Zone

A trigger amount (expressed as total protein) has been proposed for each allergen based on the lowest LOAEL dose reported in studies for each allergen (Table 2). This amount of protein has been expressed as a concentration (ppm) in a 5gm sample of food and then a 10 fold safety factor applied (as discussed above) to yield a lower transition point for each allergen.

The literature appears to show ranges for the onset of allergenic responses of between 10 and 100 fold. A second, upper transition point has been determined by applying a 10 fold increase to the lower transition point to reflect a precautionary approach. Where the highest LOAEL/NOAEL reported for an allergen is lower than the value determined by this formula (eg gluten) the reported upper LOAEL has been used instead.

Action level 2 lies between the lower and upper transition point - a precautionary cross contact statement is advised.

Action Level 3 - Red Zone

The level of allergen in protein food is above the upper threshold level - labelling of the relevant allergen as present is advised.

At the present time no additional safety factors have been proposed. In determining whether further safety factors are appropriate consideration must be given both to the uncertainties, as discussed above, and to the ability of manufacturers to analyse the allergen in food at the resulting levels as a part of plant based audits.

Table 2 - Transition points (expressed as weight of total protein) used in the determination of the VITAL Action Levels

Allergen	Transition point 1 (Action level 1 - 2) Total Protein (mg)	Transition point 2 Action level 2 - 3 Total Protein (mg)
Milk	0.25	2.5
Egg	0.1	1.0
Soy	0.5	5
Fish	1	10
Peanuts	0.1	1
Sesame Seed	0.1	1
Tree Nuts	0.1	1
Crustacea	0.1	1

Application of the VITAL Grid

Application of the VITAL Grid is set out in the VITAL Procedure and the AFGC Food Industry Guide to Allergen Management and Labelling.

REVIEW

Action levels to be reviewed six (6) monthly with the first review to occur no later than December 2007.

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