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The VITAL Scientific Expert Panel Review (VSEP)

An Allergen Bureau Presentation based on the work of the VITAL Scientific Expert Panel

November 2011

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VITAL – The Scientific Journey

- VSEP January 2011 - Collaboration
- Reviewing the Science – Methodology & Working Example
- VSEP Panel Recommendations
- VITAL & Risk
- Questions Remaining
- The VITAL Scientific Future

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VSEP – The 2011 Scientific Review Timeline

- **January –** VSEP first meeting
- **February** - FARRP supported another face to face meeting of some of the key Panel members in The Netherlands at TNO
- **February until end May** - Extensive review and collation of data by TNO and FARRP , many teleconference meetings
- **June (end)** - Preliminary recommendation's reported
- **August** - Extensive agreement achieved on 11 allergenic foods; Insufficient data for 2 foods
- **September (end) -** Report finalised
- **October (end)** - Public communication - Media Release

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VSEP January 2011 Collaboration

- The first VITAL Scientific Expert Panel (VSEP) meeting was held in Sydney on January 19-20, 2011
- Significant collaboration was required to ensure the event could proceed:
  - The Allergen Bureau;
  - FARRP (Food Allergy Research and Resource Program (University of Nebraska) and;
  - TNO (The Netherlands Organisation for Applied Scientific Research)
- Meeting focus & objective was to review and discuss Action Levels in the VITAL Grid
  - Underpinning science

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VITAL Scientific Expert Panel (VSEP)

- Scientific Expert Panel

Panel Members are:

- Dr Steve Taylor (FARRP)
- Dr Joseph Baumert (FARRP) , supported by Mr Benjamin Remington (FARRP),
- Dr Geert Houben (Program Manager Food Safety,TNO. NL)
- Dr Rene Crevel (Allergy & Immunology, Unilever)
- Dr Katie Allen (Paediatric Gastroenterologist/Allergist , Royal Chrildrens Hospital, University of Melbourne), supported by Ms Jennifer Koplin
- Dr Simon Brooke Taylor (Food Safety & Risk Analysis Consultant, Allergen Bureau)

- The VSEP received significant support from Astrid Kruizinga (TNO), Ellen Dutman (TNO) & Harrie Buist (TNO)

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VITAL Scientific Review – January Mtg

- The Panel established principles used in selecting reference doses ;
  - scientifically & clinically sound, defensible and transparent
- Determined that the *original* Action Levels in VITAL were:
  - appropriate based on available science at that time
- Relevance of Portion/Serving Size/Reference Amount
  - allergen protein expressed as mg of protein with concentration determined by using the reference amount or serving size
- Exquisitely allergic consumers will not be accounted for in VITAL , we continue to assume they do not eat processed foods

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VITAL Scientific Review – January Mtg

- Level of Acceptable Risk
  - protection for vast majority of allergic individuals
- Reference doses set with highest degree of safety
  - Increasing availability of clinical data enables the model to be applied with increasing confidence
  - Acknowledges & drives research to fill the data gaps
- Potentially opens up choice to a larger number of 'safe' foods
  - Consistent approach across industry
  - Precautionary labels applied when appropriate and in a consistent manner
- Plan is for reference doses to be subject to ongoing review

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Original VITAL Scientific Approach

- Key information taken from the FDA Threshold Working Group Report of 2006
- Used LOAELs from FDA table
- Applied an uncertainty factor (UF) to action levels set
- Expressed action levels in concentration (ppm) rather than amount of protein(mg); based on 5 g serving size **(teaspoon/mouthful)**
- Most VITAL min levels set at >2 ppm (exceptions fish, milk, soy, gluten)

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The VSEP Overarching Scientific Approach

Quantitative Risk Assessment

- The threshold needs to be *predictive* for the *entire population*
  - Representative population weighted to include individuals who react to very low amts & their counterparts who require large amts
- Statistically based risk assessment provides the ideal approach to the establishment of a population thresholds for allergenic foods
  - This type of risk assessment requires *individual threshold doses* from a sufficiently *large* number of allergic individuals
- Analysis of the clinical literature was conducted to determine if the ***quantity*** and ***quality*** of published and unpublished data was sufficient,
  - to apply RA modelling & prediction of population based thresholds

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The VSEP Methodology (ILSI – FARRP)

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Data Collection & Screening

- Reviewing data
  - Screening for NOAEL and or LOAEL on individual allergic subjects
  - Raw data on individual thresholds, taken from FARRP and TNO publications
  - Unpublished clinical data were also used from Dutch clinics and FARRP studies
- Publications looked for DBPCFC starting at low doses that potentially allowed identification of NOAELS and LOAELS for individual patients
- NOAELS & LOAELS were expressed in terms of doses of either whole food or food protein eliciting subjective or objective symptoms
  - Focus was objective symptoms as basis for the LOAEL
  - Objective symptoms, discernable to clinical observer, vomiting, Urticaria

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The Tools Applied

- Applied Interval Censoring Survival Analysis (ICSA) approach
  - Considered appropriate when the exact dose that provoked a reaction is not known, but known to fall into a particular interval (NOAEL & LOAEL)
  - Determined NOAELs and LOAELs to estimate thresholds
- Used statistical dose-distribution modelling and applied 3 different probability models: log-normal, log-logistic, and Weibull to all data sets
  - Looking for the model that provides data best fit
  - Given that the principle application lay in low dose estimations, goodness of fit in that part of the dose range is important
- From dose distribution models the eliciting dose is decided (dose predicted to provide reactions in 1, 5 and 10% of the allergic population respectively)
  - ED01, ED05, ED10, ED50, and 95% confidence intervals

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Questions that had to be addressed

- Can we combine paediatric and adult data points?
- Can we combine data from different clinics?
- Cumulative vs. discrete doses?
- Does the choice of statistical model make a difference? Application of different models for different allergens
- Does sufficient data exist to use the ED01 in every case?
  - Alternate –lower 95% confidence interval of ED05

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Working Example

Peanut

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Peanut Data

- Published studies or unpublished clinical data
- Peanut-allergic by history or other factors (skin prick tests)
- DBPCFC
- Individual NOAELs and LOAELs were expressed in terms of whole peanut (mg) or peanut protein (mg)
- Objective symptoms at doses

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Collecting & Reviewing the Data

Peanut Threshold Data Gleaned From Publications and Unpublished Clinical Records

Allergen	Study	Total No. with Objective Symptoms	Right Censored	Left Censored	Population	Reference
Peanut	Atkins et al.	2	0	0	Adults	(J Allergy Clin Immunol, 1985, 75:356-363)
	Hourihane et al.	13	11	0	Adults and Children	(J Allergy Clin Immunol, 1997, 100:596-600)
	Wensing et al.	26	20	0	Adults and Children	(J Allergy Clin Immunol, 2002, 110:915-920)
	Lewis et al.	40	0	3	Adults and Children	(Clin Exp Allergy, 2005, 35:767-773)
	Flinterman et al.	22	11	0	Children	(J Allergy Clin Immunol, 2006, 117:448-454)
	Leung et al.	23	8	1	Adults and Children	(NEJM, 2003, 348:986-993)
	Oppenheimer et al.	4	0	0	Adults and Children	(J Allergy Clin Immunol, 1992, 90:256-262)
	Nelson et al.	12	0	1	Adults	(J Allergy Clin Immunol, 1997, 99:744-751)
	Nancy *	283	10	7	Adults and Children	(Food and Chem Tox, 2010, 48:814-819)
	Anagnostou et al.	18	0	7	Adults and Children	(Clin Exp Allergy, 2009, 39:1937-1958)
	Clark et al.	5	0	1	Children	(Allergy, 2009, 64:1218-1220 and Clin Exp Allergy, 2008, 38:1978-1995)
	Nicolaou et al.	10	0	2	Children	(J Allergy Clin Immunol, 2010, 125:191-197)
	Blumchen et al.	22	0	2	Children	(J Allergy Clin Immunol, 2010, 126: 83-91)
	Wainstein et al.	8	0	0	Children	(Pediatr Allergy Immunol, 2010, 21:603-611)
	Patriarca et al.	1	0	0	Adults	(Digestive Diseases and Sciences, 2006, 51:471-473)
	WKZ **	85	5	1	Children	(Unpublished Clinical Data)
	UMCU ***	42	17	0	Adults	(Unpublished Clinical Data)
	UMCG****	135	50	5	Children	(Unpublished Clinical Data)
	Total	**750**	**132**	**30**		

* Published only in summarized form

**WKZ – Wilhelmina Kinderziekenhuis (children's hospital of the UMCU, The Netherlands)

***UMCU – University Medical Center Utrecht - Includes Peeters et al. (Clin Exp Allergy, 2007, 37:108-115)

****UMCG – University Medical Center Gronigen

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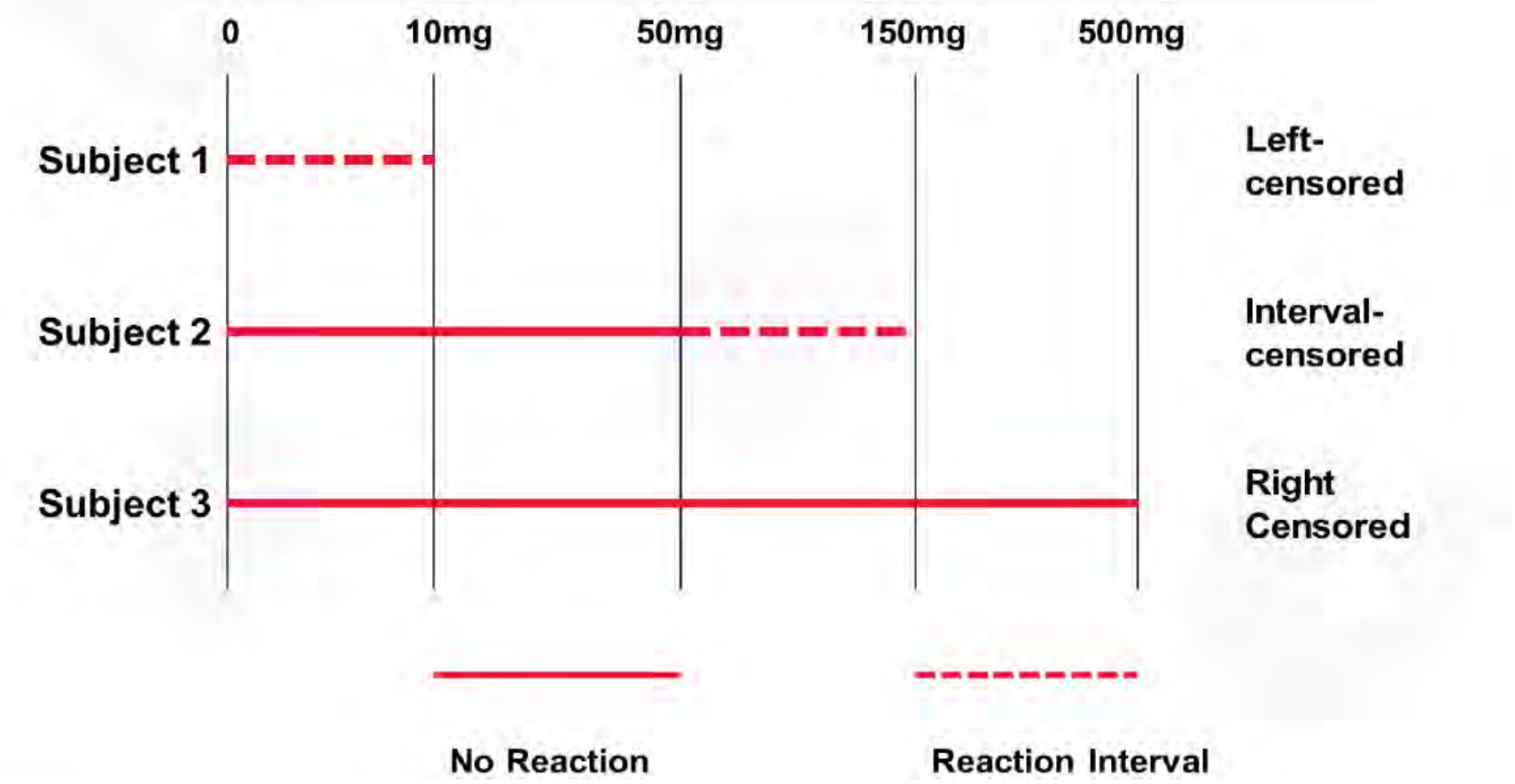
The Tools Applied

Interval-Censoring Survival Analysis



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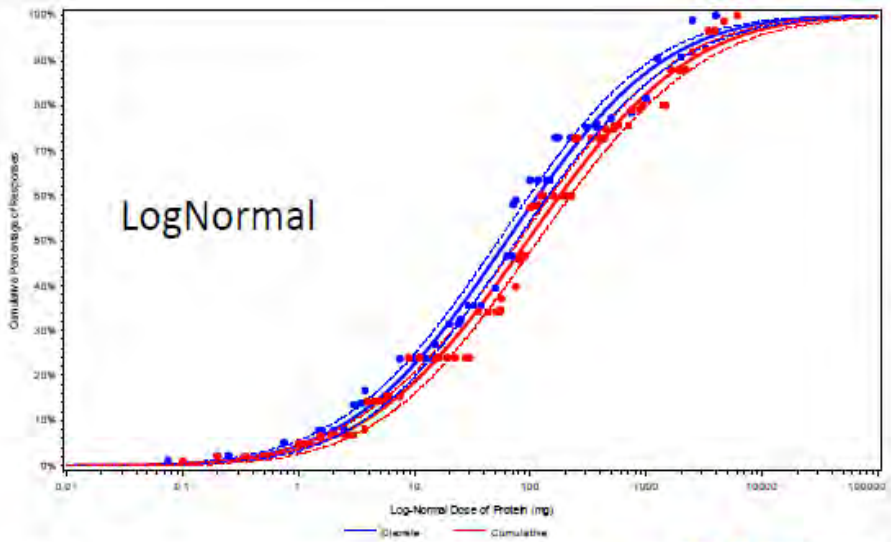
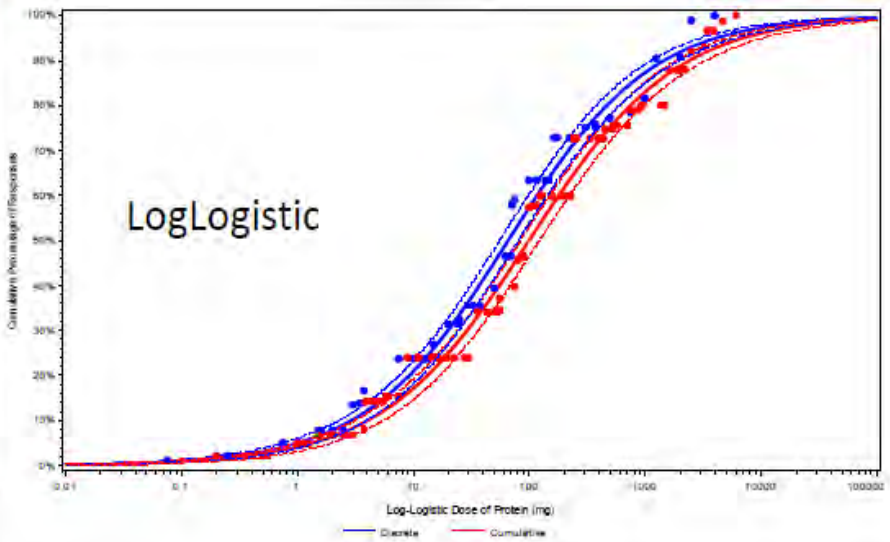
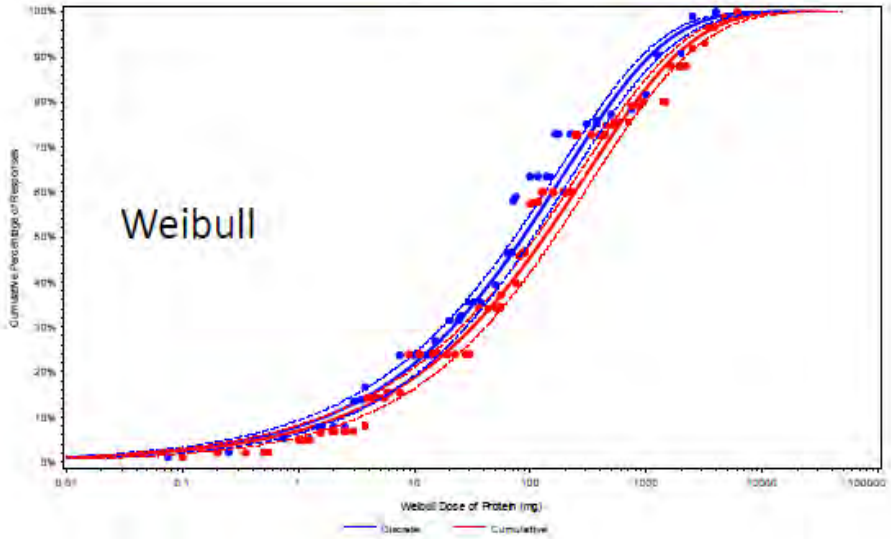
The Tools Applied







Adults and Children curve

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The Tools Applied

Eliciting Dose – ED1

Individual data	Total Number of Data Points (RT, LT)	Model	ED1	LCI	UCI
Data / pooled children	585 (79, 36)	llog	0.14	0.085	0.23
		lnor	0.27	0.18	0.4
		weib	0.017	0.008	0.034
data / pooled adults	99 (44, 1)	llog	0.21	0.045	1
		lnor	0.57	0.17	1.9
		weib	0.069	0.01	0.5
data / pooled children & adults	750 (132, 41)	llog	0.1	0.062	0.16
		lnor	0.22	0.15	0.32
		weib	0.013	0.007	0.024
Cumulative data	**Total Number of Data Points (RT, LT)**	**Model**	**ED1**	**LCI**	**UCI**
Data / pooled children	585 (79, 25)	llog	0.18	0.11	0.3
		lnor	0.34	0.23	0.51
		weib	0.021	0.01	0.042
data / pooled adults	99 (44, 1)	llog	0.26	0.05	1.3
		lnor	0.72	0.21	2.5
		weib	0.076	0.01	0.59
data / pooled children & adults	750 (132, 30)	llog	0.13	0.08	0.2
		lnor	0.28	0.19	0.4
		weib	0.015	0.01	0.029

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Threshold data points for each Allergen

Allergen	Total No. with Objective Symptoms	Right Censored*	Left Censored**	Population
Peanut	750	132	30	Children and Adults
Milk	351	19	59	Children and Adults
Egg	206	33	24	Children and Adults
Hazelnut	202	67	4	Children and Adults
Soybean	80	28	6	Children and Adults
Wheat	40	1	5	Children and Adults
Cashew	31	16	1	Children
Mustard	33	10	2	Children and Adults
Lupin	24	7	2	Children and Adults
Sesame	21	1	2	Children and Adults
Shrimp	48	26	0	Adults
Celery	39	4	15	Children and Adults
Fish	19	2	6	Children and Adults

*Number of right-censored subjects (NOAEL = highest challenge dose; LOAEL set to infinity).
**Number of left-censored subjects (NOAEL set at zero; LOAEL = lowest challenge dose).

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VSEP Recommendations – Reference Doses

Allergen	Protein Level (mg)
Peanut	0.2
Milk	0.1
Egg	0.03
Hazelnut	0.1 (VITAL – Level used as generic tree nut value)
Soy	1.0 (VITAL – Soy protein isolates not soy milk)
Wheat	1.0 (VITAL – GCC (Coeliac & wheat allergic population)
Cashew	2.0 *(VITAL - Hazelnut as generic tree nuts value)
Mustard	0.05
Lupin	4.0
Sesame	0.2
Shrimp	10.0
Celery	NA
Fish	NA (VITAL – original VITAL value applied)

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VITAL & Risk

- VITAL approach used all of the existing published data plus some unpublished data -**Unpublished data needs to be published**
- VITAL grid levels will protect 95-99% of allergic consumers (99% is desirable when sufficient data exists to allow statistically sound estimates at this level)
- Exquisitely sensitive allergic consumers may not be fully protected by the VITAL grid levels (assume do not consume packaged foods)
- No additional uncertainty factors needed because of use of ED01 or lower 95% confidence interval of ED05

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VITAL & Risk (cont)

- Risk of mild, transitory objective reactions typically requiring no pharmacological intervention
- Allergic populations studied appear to be representative or skewed toward more highly sensitive (referral clinics, immunotherapy studies)

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Remaining Questions

- Challenge data are not available for some commonly allergenic foods (e.g. almond, walnut) –how to establish action levels?
- Insufficient data for celery and fish, how to drive the research gaps?
- Challenge data exists for modest numbers of patients for other commonly allergenic foods (e.g. sesame seed, lupin, shrimp, mustard)
  - How to drive the research gaps?
- Species of fish and crustacea? Very limited data and the big unknown!

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Continuing the VITAL Scientific Journey

- The Allergen Bureau plan is to maintain the VSEP ongoing and continue to invest in the VITAL future
- New science and data needs to continue to be considered
- The Allergen Bureau objective is to support initiatives, projects and collaborations where possible to drive the research gaps
- Currently reviewing the possibility of collaboration with the EU
- The Allergen Bureau continue to stay closely linked in to the ILSI Thresholds to Action Levels Group

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VSEP - What does Success look like?

- Reference doses determined for each of the top food allergens, Research gaps continue to be addressed
- Standardised methodology or approach to determine appropriate reference dose information, consistent application
- The relevance and importance of Reference Amounts or Serving Size in determining Action Levels, clarity around actual consumption data
- Food industry adoption and implementation of the reference dose, reference amount, action level precautionary labelling risk assessment
- Consistent application globally to drive safe food choices, protection for the allergic consumer means protection for our industry'
- International recognition by the scientific community

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Dream becoming a Reality

Global Harmonised Action Levels Within Our Reach Imagine That!

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Thank you

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