Chapter | five

Thresholds or 'How Much Is Too Much?'

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CHAPTER OUTLINE

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INTRODUCTION

Since the emergence of food allergy as a public health issue in the early to mid 1990s, the question 'how much is too much' has been at the forefront of the mind of risk assessors and regulators, as well as allergic consumers and clinicians. Initial impressions from anecdotal reports suggested that thresholds were extremely low, although with hindsight such reports inevitably presented a biased picture focused on the more interesting cases. It was soon recognized that they formed a poor basis for risk assessment, and efforts began to generate clinical data [1]. In parallel, initiatives were set up to systematically gather available data, most of which were unpublished [2]. The latter effort has since been updated by the US FDA's Threshold Working Group [3,4]. This work revealed very significant data gaps but also highlighted some early conclusions about the difficulties in determining population thresholds, which are critical to the public health dimension. They thus also spurred new lines of investigation into methods to use these data effectively, while also highlighting considerations that were critical to data quality and usability.

The EuroPrevall project, which ran from 2005 to 2009, built on these earlier observations to deliver one of its core objectives, namely data and tools to improve food allergy and food allergen management. Actual data on thresholds were a critical element of these data, but just as important was the application and further improvement of new methodologies to analyze such data at the population level. A strong emphasis on high quality of data ran through the strategy of the project, delivered through rigorously defined protocols, applied to a consistent standard and with a high degree of resolution within the data. This chapter describes the unique features of the EuroPrevall strategy, linking it to the pre existing data and knowledge. It also considers their contribution to delivering the objectives of the project and the way that they will thereby help to improve the management of allergens from a public health perspective.

WHAT IS MEANT BY THRESHOLDS IN THE CONTEXT OF FOOD ALLERGY AND ALLERGENS?

The Concise Oxford English Dictionary (ninth edition) defines threshold (physiology) as 'a limit below which a stimulus causes no reaction', which operationally translates to a dose at, or below which, a response is not seen in an experimental setting [5].

Individual clinical thresholds as determined in a challenge study lie between the highest dose observed not to produce any adverse effect (No Observed Adverse Effect Level [NOAEL]) and the lowest dose to produce an adverse effect (the Lowest Observed Adverse Effect Level [LOAEL]). In food allergy, the term 'threshold' has often been approximated to the LOAEL, although the accuracy of this approximation depends on dose spacing. Allergic people respond over a very wide range of doses, and this, together with the limitations inherent in studies of human beings, makes the

prospect of obtaining absolute experimental thresholds for food allergens for human populations a remote possibility.

Allergic responses, in common with other immune responses, consist of two phases: sensitization and elicitation. Thresholds probably apply to both phases. However, little is known about thresholds of sensitization to food proteins in human beings, and in practice the term 'threshold' in food allergy is largely used in relation to the elicitation phase. This chapter therefore only addresses thresholds of elicitation and furthermore limits itself to IgE-mediated reactions, which are those that can produce the most acutely life-threatening manifestations.

Thresholds exist at both an individual and a population level. Individual thresholds can be estimated experimentally, but this does not hold in practice for population thresholds. The term 'threshold' is also invested with different meanings in different contexts (e.g., regulatory thresholds and analytical thresholds), and the term 'minimum eliciting dose' is therefore preferred [6]. In modeling the distribution of minimum eliciting doses for any given allergenic food, the term Eliciting Dose (EDp) can thus be used to designate the amount of allergen predicted to produce a reaction in a defined proportion (for instance 0.5, 1, or 5%: ED0.5, ED01, or ED05) of the allergic population, to distinguish it from experimentally determined thresholds. The EDp can be considered as a threshold for a defined proportion of the allergic population.

THRESHOLDS BEFORE EUROPREVALL: WHAT DATA WERE AVAILABLE AND HOW USEFUL WERE THEY FOR RISK ASSESSMENT?

What Data Existed on Thresholds?

Case reports and series show that exposure to small quantities of an offending food can sometimes elicit a severe allergic reaction in a sensitized individual [7,8]. However, these studies provide little quantitative information. Diagnostic, double-blind, placebo-controlled food challenges (DBPCFC), in use since the 1970s [9,10], have generated more quantitative information on thresholds of reactivity. However, the design of these studies resulted in a high proportion of first dose reactors, which made them unsatisfactory for modeling the distribution of minimum eliciting doses and more generally for risk assessment [11]. Taylor et al. [2], in an analysis of data produced up to the late 1990s, found that several hundred patients had been challenged at lower doses with cows' milk [n=598], egg [n=782], and peanuts [n=663], as well as smaller numbers with other allergenic foods. However because these data were often obtained by means of different protocols, the estimation of a threshold dose was very difficult. Studies designed specifically to establish low dose reactivity did not appear until the late 1990s [1].

The most reliable and plentiful data on minimum eliciting doses (MEDs) result from challenge studies performed in peanut allergic patients. These data originated from a range of studies, including diagnostic challenge series

using a low dose challenge methodology, low dose challenges designed to determine MEDs, but also immunotherapy studies. Data from these various sources, together with previously unpublished data, covering altogether over 450 patients, proved suitable for dose distribution modeling [12,13]. These analyses revealed ED10s (i.e., the doses estimated to give a reaction in 10% of peanut allergic individuals) on the order of 4 mg of peanut protein for the populations in question. Very recently, an extensive analysis of published and unpublished low dose challenge data on 13 allergenic foods was conducted by an Expert Panel convened by the Australian Allergen Bureau to review the action levels used in their Voluntary Incidental Trace Allergen Labeling (VITAL) scheme, which is described in further detail below.

The VITAL Scientific Expert Panel and Thresholds

The VITAL scheme is a comprehensive system for allergen management developed by the Allergen Bureau of Australia. It was first introduced in 2007 and was recently the subject of an extensive review and overhaul. It is beyond the scope of this chapter even to give an overview of the system. However, thresholds for labeling have been a critical and integral component of the system from the start and were therefore included in the recent review. Unlike other elements of the system, the Allergen Bureau decided that this review should be conducted by a panel of independent, internationally recognized experts.

In 2011, an extensive analysis of published and unpublished low dose challenge data on 13 allergenic foods was conducted by the VITAL Scientific Expert Panel for the Australian-New Zealand Allergen Bureau [14]. The VITAL Scientific Expert Panel convened by the Allergen Bureau is founded on a collaboration between the Food Allergy Research and Resource Program (FARRP, University of Nebraska, US) and the Netherlands Organization for Applied Scientific Research (TNO, Zeist, The Netherlands) together with other experts. The panel had access to and analyzed threshold data from published literature, unpublished clinical records in the Netherlands and Germany, and partially completed FARRP studies and concluded that sufficient data exist for most major allergenic foods of concern for the distribution of MEDs in the various populations of individuals who had undergone food challenges to be modeled statistically. The resulting dose distribution curves enable the establishment of an eliciting dose for each allergenic food (EDp) at which a certain proportion of the allergic population (p) would be likely to react. This approach was used to establish Eliciting Dose (ED) values to be used as reference doses for guiding decision making regarding the use of precautionary labeling ('may contain' labeling), which warns of the possible presence of small amounts of unintended allergen.

MED distributions based on both discrete and cumulative doses were modeled using three different statistical models (log normal, log logistic, and Weibull). ED values for all three models were determined, with preference being given to the model with the best fit at low doses, as determined by statistical and visual examination. Where sufficient data existed, in addition to the

combined data, dose distributions were modeled separately for infants and children versus adults, in addition to the whole dataset. The challenge doses were normalized in all cases to mg of protein from the allergenic food.

Sufficient data from the available studies existed to allow dose distribution modeling for 11 major allergenic foods (see Tables 5.1 and 5.2). For four allergens, the number of data points was sufficiently abundant (good to excellent data set) to define ED01 values reliably (i.e., without recourse to low dose extrapolation beyond the experimental data set). For seven allergens with a dataset based on fewer individual MEDs, but still sufficient for statistical modeling, ED01 values sometimes might be less reliable, and the lower confidence interval of the ED05 was also considered as the basis for the

Table 5.1 Summary of VITAL Scientific Expert Panel Recommendations

Allergen	Reference Dose (mg Protein)	Basis of Reference Dose	Quality of Database**
Peanut	0.2	ED01	Excellent
Milk	0.1	ED01	Excellent
Egg	0.03	ED01 and ED05 95% lci*	Excellent
Hazelnut	0.1	ED01 and ED05 95% lci	Good
Soy	1	ED05 95% lci Note: this level may not completely protect certain individuals sensitive to soy milk	Sufficient
Wheat	1	ED05 95% lci Note: wheat-allergic consumers would be protected by foods containing < 20 ppm gluten	Sufficient
Cashew	2	ED05 95% lci	Sufficient
Mustard	0.05	ED05 95% lci	Sufficient
Lupin	4	ED05 95% lci	Sufficient
Sesame	0.2	ED05 95% lci	Marginally sufficient
Shrimp	10	ED05 95% lci	Marginally sufficient
Celery	n/a		Insufficient
Fish	n/a		Insufficient
Other tree nuts (walnut, pecan, almond, pistachio, brazil nut, macadamia, pine nut)			Insufficient

**Lower confidence interval*
***The classification of quality reflects the abundance of data and its distribution across the dose range (Allergen Bureau 2011)*