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Food allergy population thresholds: An evaluation of the number of oral food challenges and dosing schemes on the accuracy of threshold dose distribution modeling

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ABSTRACT

For most allergenic foods, limited availability of threshold dose information within the population restricts the advice on action levels of unintended allergenic foods which should trigger advisory labeling on packaged foods.

The objective of this paper is to provide guidance for selecting an optimal sample size for threshold dosing studies for major allergenic foods and to identify factors influencing the accuracy of estimation. A simulation study was performed to evaluate the effects of sample size and dosing schemes on the accuracy of the threshold distribution curve. The relationships between sample size, dosing scheme and the employed statistical distribution on the one hand and accuracy of estimation on the other hand were obtained. It showed that the largest relative gains in accuracy are obtained when sample size increases from $N = 20$ to $N = 60$. Moreover, it showed that the EuroPrevall dosing scheme is a useful start, but that it may need revision for a specific allergen as more data become available, because a proper allocation of the dosing steps is important.

The results may guide risk assessors in minimum sample sizes for new studies and in the allocation of proper dosing schemes for allergens in provocation studies.

1. Introduction

Clinical oral food allergy provocation studies and the threshold dose information they produce provide valuable information on the sensitivity of the allergic populations/patients. Several studies with a variety of allergenic foods tested show that the individual threshold, or lowest observed adverse effect level (LOAEL), varies within the food allergic population (Ballmer-Weber et al., 2007; Wensing et al., 2002a; Wensing et al., 2002b). The dose distribution studies of Taylor et al. (2009, 2010) observed a variation of 5–6 orders of magnitude within the peanut allergic population. Studies with other allergens also show this wide variation in clinical LOAELs (Blom et al., 2013). Thus all individuals within an allergic population are not at the same level of risk of having an allergic reaction.

Threshold-based risk approaches have long been used for the management of chemical and microbial hazards in food but have not been widely adopted by regulatory agencies in the management of food allergens (EU, 2003; Kroes et al., 2000; Lammerding and Fazil, 2000; Larsen, 2006; Notermans et al., 1995). Food allergen thresholds have different meanings to different stakeholders. To the food allergic consumer, their personal threshold or LOAEL is the smallest amount of food required to cause an allergic reaction. The population threshold could be the amount of food required to cause a reaction in the most sensitive individual or in a determined percentage of the food allergic population. To the food industry and regulatory bodies, the term threshold could determine how much allergen would trigger a product recall if unlabeled or when to place an advisory statement on the label if allergens are occasionally present due to cross-contact despite industry's best efforts to minimize the unintended presence of allergen through good manufacturing and cleaning practices. The

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; NOAEL, no observed adverse effect level; LOAEL, lowest observed adverse effect level; ED, eliciting dose.

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importance of food allergy as a public health and food safety issue has placed pressure on the food industry and regulatory agencies to implement threshold-based strategies to protect the food allergic consumer.

In the absence of guidance from public health authorities regarding thresholds, the food industry has implemented the widespread use of various forms of voluntary advisory or precautionary "may contain" labeling in an attempt to manage the risk and protect food-allergic consumers. However, as a result of the widespread use of advisory labels, the quality-of-life of food-allergic consumers has decreased due to the ever decreasing number of food choices available and some are ignoring these advisory statements (Hefle et al., 2007; Hourihane et al., 2011). Additionally, the widespread use of advisory labeling has led to varying advice within the medical community on whether patients should avoid all foods with advisory labeling (Koplin et al., 2010; Vierk et al., 2007). Acceptance of management thresholds by regulatory authorities could benefit allergic consumers as there would be more transparency in the use of advisory labeling by food industry but they should never be advised to ignore advisory statements on package labels (Taylor and Hefle, 2006). All stakeholders present in a workshop organized and reported by Madsen et al. (2012) (regulators, food industry, clinical researchers and healthcare professionals, and food-allergic consumers) agreed it is essential to address the current lack of action levels and thresholds for food allergen labeling, but it is difficult to define and quantify a level of tolerable or accepted risk (Madsen et al., 2012). There is an obvious need for research and scientific advancement in the area of food allergen thresholds.

The threshold dose information is the base for formulating ideas to define action levels for precautionary warnings for major allergens. The FDA Threshold Working Group and others have agreed that allergic population thresholds and a quantitative risk assessment-based approach provides the strongest, most transparent scientific analyses to establish thresholds for the major food allergens (Gendel et al., 2008; Madsen et al., 2009; Spanjersberg et al., 2007). However, the quantitative (probabilistic) approach has only recently been applied to food allergens (Kruizinga et al., 2008; Rimbaud et al., 2010; Spanjersberg et al., 2010; Spanjersberg et al., 2007). The FDA Threshold Working Group stated that data available in 2006 were not sufficient to meet the requirements of the quantitative approach and that a research program should be initiated to develop applicable risk assessment tools and to acquire and evaluate the clinical and epidemiological data needed to support the quantitative risk assessment-based approach (Gendel et al., 2008). Recent work by the Netherlands Organisation for Applied Scientific Research (TNO) in the Netherlands and the Food Allergy Research and Resource Program (FARRP) at the University of Nebraska utilized published low dose double-blind, placebo-controlled oral food challenges (DBPCFC) for 13 priority allergens and additional unpublished data from allergy clinics in Europe to accumulate over 1800 individual allergic thresholds from DBPCFCs (Taylor et al.,2014; Allen et al., 2014). In the review of the Voluntary Incidental Trace Allergen Labelling program (VITAL®), the team of experts rigorously searched literature and collected unpublished threshold information for peanut, egg, soy flour, and 10 other priority allergenic foods with the purpose of threshold dose distribution modeling. The collation of all threshold data showed that for some allergenic foods, threshold dose information was available for more than 200 individuals (peanut, hazelnut, milk and egg), whereas for many other allergenic foods smaller datasets (<80) were available (Taylor et al., 2014; Allen et al., 2014). For each dataset, the individual No Observed Adverse Effect Levels (NOAEL) and the LOAELs were combined to derive population threshold dose distribution curves for each allergenic food using the dose distribution approach as described in Crevel et al. (2008), together with survival analysis methods as used in Taylor et al. (2009, 2010). This approach is widely accepted as one that uses the available data most effectively (Gendel et al. 2008; Madsen et al., 2009). In selecting the eliciting dose (ED) for the allergic population (in which the EDx represents the dose at which *x*% of the allergic population would be expected to react with objective symptoms), weight was given to the goodness of fit for each parametric model (determined by the log likelihood) as well as visual examination of the fitted probability distribution.

Threshold dose distributions are a crucial component in the quantitative risk assessment to estimate the number of allergic reactions within the allergic population. Threshold-based assessments provide quantitative insight to the health risk associated with the level of allergenic food present in a typical food product (Spanjersberg et al., 2010; Rimbaud et al., 2013; Remington et al., 2013). To generate more fundamental scientific underpinning for the number of data points desirable to establish sound regulatory threshold distributions for food allergy, we set up a simulation study using the peanut, egg, and soy flour threshold data as reference distributions to investigate the effects of the number of allergic individuals included in the population threshold analysis (*N*), censoring, and the dose scheme used at challenge.

2. Methods

2.1. Reference dataset

The reference distributions for the simulation study were based on discrete NOAEL and LOAEL values from 750 individual DBPCFCs for peanut, 206 for egg, and 51 for soy flour (Allen et al., 2014; Taylor et al., 2014). The population thresholds for peanut, egg, and soy flour were used as model allergens due to their differences in population sensitivity (egg > peanut > soy flour). Three commonly used distribution functions; the log-normal, log-logistic and Weibull distribution, were fitted to this data using PROC LIFEREG in SAS v9.1 (SAS Research Institute). We do acknowledge that the VITAL® Scientific Expert Panel determined that the Weibull distribution did not provide a good fit to the actual threshold data for peanut and was not used in the derivation of a reference dose for peanut. However, this paper deals with the general task of studying sample size and dosing scheme effects and therefore it is important to include the Weibull distribution as a reference distribution. From the estimated distributions, the 1st percentile (ED01), the 5th percentile (ED05), the 10th percentile (ED10) and the 50th percentile (ED50) (the dose at which 1%, 5%, 10% or 50% of the allergic population would be predicted to react with objective symptoms) were obtained for peanut (Table 1), egg (Table 2), and soy flour (Table 3).

Those estimated distributions are used as reference distributions in the simulations presented below. For the purpose of the simulations, it will be assumed that the selected reference distribution is the true distribution to be recovered with a selected sample size and dosing scheme. Note that there is therefore no relationship with the determination of the best fitting distribution for the analysis of a specific data set at hand.

2.2. Factors varied in the simulation study

Based on information of historical dose–response studies, the following factors were identified that are important in the modeling of the threshold distribution and estimation of the ED's.

Distribution: The statistical distribution that was fitted to the data is often one of the following three parametric survival models: the log-logistic (LL), the log-normal (LN), or the Weibull (WB) distribution. The behavior in the tails of those distributions may differ (see Fig. 1 and Tables 1–3), and therefore the distribution chosen is a relevant factor for estimating the EDs.

Dosing scheme: The dosing scheme in a threshold study is an important factor because it determines the range covered and the step sizes taken in the dosing levels. To investigate the effect of different dosing levels, four dosing schemes were developed based on the dosing scheme used in the clinical challenges associated with the EuroPrevall research project, a multi-center study on the prevalence, cost, and basis of food allergy in Europe (Defernez et al., 2013). The number of dosing levels was bounded by 9, which corresponds to the maximum number of escalating doses of allergenic food a clinician can typically administer to a patient on one day. The following dosing schemes were applied in the simulations:

- Normal EuroPrevall (NEP): a low-dose clinical consensus protocol for diagnosis representing maximum coverage of the dosing scale as found in the empirical data (Crevel et al., 2008; Defernez et al., 2013). The dosing levels are 0.003, 0.03, 0.3, 3, 30, 100, 300, 1000 and 3000 mg protein from the allergenic source.

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