

Soy in wheat – Contamination levels and food allergy risk assessment

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ABSTRACT

In the United States, packaged food ingredients derived from allergenic sources must be clearly labeled. However, no requirement exists to declare the presence of residues of raw agricultural commodities due to agricultural commodity comingling. Clinical reports of allergic reactions to undeclared soy in wheat-based products do not exist suggesting that a rather low degree of risk is posed by wheat-based products that are comingled with soy. Detectable soybean residues (>2.5 ppm soy flour) were found in 62.8% of commercially available wheat flours at concentrations of 3–443 ppm soy flour (1.6–236 ppm soy protein). Conservative probabilistic risk assessments predict a risk of allergic reaction among the most sensitive soy-allergic individuals of 2.8 ± 2.0 per 1000 soy-allergic user eating occasions of foods containing wheat flour. However, the predicted reactions occur at exposure levels below the lowest eliciting dose observed to provoke objective reactions in clinical oral soy challenges. Given this low level of predicted risk and the lack of evidence for allergic reactions among soy-allergic consumers to wheat-based products, the avoidance of wheat-based products by soy-allergic consumers does not appear to be necessary.

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1. Introduction

Recent studies estimate that 4–10% of children and 3–4% of adults are affected by food-induced allergic reactions (Branum and Lukacs, 2009; Osborne et al., 2011; Rona et al., 2007; Sicherer and Sampson, 2010). Soy is one of the most common allergenic foods in children, and soy allergy can be severe (Sicherer and Sampson, 2010). Soy-allergic consumers are advised to adhere to a strict avoidance diet and carefully read ingredient labels of all foods (Hefle et al., 2007; Pieretti et al., 2009; Taylor et al., 1986). The Food Allergen Labeling and Consumer Protection Act (FALCPA) was passed in 2004 by the United States Congress to protect allergic individuals from unclear or unlabeled products and became effective January 1, 2006 (FDA, 2006). Although ingredients derived from commonly allergenic sources must be labeled in clear terms when added to food, raw agricultural commodities are exempt from FALCPA (FDA, 2006). Due to the nature of agricultural production in the United States and worldwide, raw agricultural commodities are often comingled with other agricultural commodities during harvest, transport, and storage with shared equipment and facilities. The United States Department of Agriculture (USDA) Grain Inspection Handbook allows up to 10% of other grains with established standards to be present in wheat (USDA, 2004). Other grains with established standards include barley, canola, corn, flax-

seed, oats, rye, sorghum, soybeans, sunflower seed, and triticale (USDA, 2004). The 10% level equates to 100,000 parts per million (ppm) or 100,000 mg/kg ($\mu\text{g/g}$) of other grains and would cause visual contamination within containers of wheat. The economics of buying and selling wheat have kept commodity comingling well below these allowed limits as food processors demand a cleaner, higher grade of wheat. However, the extent of the risk from commodity comingling to allergic consumers has not been investigated.

The issue of soy in other grains has become an issue for food safety inspection as highlighted by numerous food alerts within the European Union Rapid Alert System for Food and Feed (RASFF) and the Canadian Food Inspection Agency (CFIA). The Food Safety Authority of Ireland has issued multiple food alerts for the presence of soy in wheat and corn based products (white bread flour, flour and corn tortillas, corn chips, and a batter mix) (RASFF Reference 2011.0015; 2011.0019; 2011.0022; 2011.0023; 2011.0215). The CFIA also issued a food recall for a wheat-based cereal due to undeclared soy (Reference Number: 6848). Despite the lack of consumer complaints associated with this cereal, products were recalled. In all likelihood, this cereal product has been produced for years with similar levels of soy. While levels of soy and other grains are known to occur in grain-based products, few studies have reported the levels of allergenic contaminants in agricultural commodities or finished products manufactured from these commodities. One exception is gluten, in large part due to “gluten-free” labeling, with North American levels of gluten contami-

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nation in other grains reported by multiple studies. Thompson et al. (2010) reported gluten contamination in 9 of 22 (41%) inherently gluten-free grain samples with levels up to 2925 ppm gluten. In a study by Health Canada, Koerner et al. (2011) reported 117 of 133 (88%) retail oat products contained levels up to 3784 ppm gluten. However, only one oat variety with a “gluten-free” label was tested and it was consistently below the limit of quantitation for gluten. Recent IgE-mediated allergic reactions due to commodity contamination of wheat have led the CFIA to encourage manufacturers and importers of grain-based products to inform consumers and transition towards the inclusion of precautionary labeling (a ‘may contain wheat’ statement) on their products containing cereal grains, such as oats or barley, to indicate the potential presence of wheat at low levels (CFIA, 2011). Conversely, Health Canada has released guidance stating exposure to soy in grain-based foods is not likely to represent a health risk for soy-allergic individuals and advised the industry not to use advisory labeling for soy (Health Canada, 2013). Other countries have attempted to establish action levels for undeclared allergens including cross contamination of other grains in products and commodities. Switzerland has defined an action limit of 1000 ppm for allergens. This limit states that if unavoidable, contamination above 1000 ppm must be declared as an ingredient, but contamination below 1000 ppm may be declared if desired (Kerbach et al., 2009). Levels of 1000 ppm may provide enough protein (low mg doses) to cause reactions at moderate consumption levels in multiple foods (Taylor et al., 2004). Japan has taken a stricter approach and limited undeclared allergens including commodities to 10 ppm in foods (Kerbach et al., 2009). Commodity grain shipments may be expected to exceed this Japanese limit but with unknown frequency.

The actual levels of other grains, including soy, in wheat are likely much lower than the 10% allowed by the USDA Handbook. This study surveyed wheat flours available at local grocery stores for the presence of soy. The resultant potential risk to soy-allergic consumers of these products is determined.

2. Materials and methods

2.1. Wheat flour market survey

A total of 35 wheat flour products were purchased in 2010 from grocery stores in Lincoln, Nebraska, USA. Products included all-purpose, whole wheat, white wheat, bread, and pastry flours. A representative sample from each package was homogenized and then analyzed for the presence of soybean using a commercial enzyme-linked immunosorbent assay (Neogen Veratox® Soy Allergen kit) with a lower limit of quantification of 2.5 ppm soy flour (µg/g). Samples were prepared and analyzed according to instructions provided with the kit. Results were converted to ppm soy protein for quantitative risk assessment by assuming that soy flour contains 53% protein (Ballmer-Weber et al., 2007).

2.2. Threshold doses

Individual threshold doses were obtained from published, double-blind, placebo-controlled food challenges (DBPCFC) of 43 soy-allergic individuals (Ballmer-Weber et al., 2007; Fiocchi et al., 2003; Magnolfi et al., 1996; Zeiger et al., 1999) as based on objective symptoms as previously described (Taylor et al., 2009). Log-Normal, Log-Logistic, and Weibull probability distribution functions were fitted to the lowest-observed-adverse-effect-levels (LOAELs) and/or no-observed-adverse-effect-levels (NOAELs) from each individual to describe the population threshold dose expressed as mg soy protein. Simple fit statistics (AIC, AICC, BIC) and the visual fit were similar for all three distributions. No biological basis exists upon which to select any one of the distributions over the others; the Log-Normal distribution was chosen for use in all probabilistic risk assessments.

2.3. Wheat flour consumption

The presence of soy residues in wheat flour resulting from commodity commingling was used to assess the risk to soy-allergic consumers across a broad spectrum of wheat flour-based foods. Consumption of wheat flour was based on individuals in the United States and extracted from the 2003–2006 National Health and Nutrition Examination Surveys (NHANES) of the U.S. Department of Agriculture (USDA). Indi-

viduals who did not complete both days of the survey were excluded from the analysis. Wheat flour consumption was estimated using the Foods Analysis and Residue Evaluation (FARE™) program from Exponent® with an eating occasion being defined as 1 h of consumption. Conservatively, this study estimated that 1 h of consumption was equal to one eating occasion. The recipes in FARE™ are based on the recipes provided by USDA with modifications to analyze individual components of foods. Log-Normal, Log-Logistic, and Weibull probability distribution functions were fitted to reported wheat flour consumption data using the LIFEREG procedure in SAS. Simple fit statistics (AIC, AICC, BIC) were similar but the Weibull distribution had a better visual fit and was chosen for use in probabilistic risk assessments.

Chocolate chip cookies were used as a model food for risk assessment of a single food category. Consumption of chocolate chip cookies was based on the 2003–2006 NHANES survey. Chocolate chip cookies are estimated to be 20% wheat flour by weight after analyzing the weights of ingredients in popular chocolate chip cookie recipes from the USDA National Nutrient Database. Simple fit statistics (AIC, AICC, BIC) and the visual fit were similar for the Log-Normal, Log-Logistic, and Weibull distributions. The Log-Normal distribution was chosen to represent chocolate chip cookie consumption in the risk assessment.

As no consumption database exists solely for allergic consumers, the assumption was made that allergic and non-allergic individuals consume wheat flour and chocolate chip cookies at the same rate and their reasons for non-consumption are the same.

2.4. Quantitative risk assessment of soy in commercially available wheat flours

The probabilistic risk assessment model for food allergens utilizes the Monte Carlo simulation to quantitatively estimate the risk of a specific product for a food allergic population (Kruizinga et al., 2008; Spanjersberg et al., 2007). Briefly, statistical distributions can be fitted to input data for prevalence of soy allergy, soy thresholds, wheat flour consumption patterns, and the concentrations of soy in wheat flour samples for use in a Monte Carlo simulation. The current risk assessment incorporates a Bayesian framework into a 2nd order Monte Carlo simulation (Adapted from Rimbaud et al. (2010)) to estimate the risk of an allergic reaction from consumption of undeclared soy in wheat flours (Fig. 1). The simulation will set and hold distribution parameter inputs for a single run and then resample to achieve a new set of parameter inputs for the next run. Each run consists of 10,000 iterations that randomly sample from each set distribution and match if the individual is allergic, a consumer of the type of product, and if the product contains soybean to determine if there is a risk of an allergic reaction. An individual will have a predicted allergic reaction if the predicted consumed amount and concentration of soybean lead to a dose over the predicted allergen threshold for that individual. The process repeats until 50 runs have been completed for a total of 500,000 iterations. All statistical tests were done in SAS (version 9.2).

The threshold dose of an allergic individual can be estimated from the predictive posterior of the threshold variable, which is modeled by a Log-Normal dose-response distribution with normal prior distributions for the mean and standard deviation parameters. The normal prior distributions were created using the calculated estimate and standard error for the mean and standard deviation parameters from the LIFEREG procedure in SAS. Similarly, the wheat flour consumption amount can be estimated from the predictive posterior of the consumption variable and is modeled by a Weibull distribution with normal prior distributions for the mean and standard deviation parameters.

The number of wheat flour consumers in a population can be modeled by a binomial distribution of which the parameters are the prevalence of wheat flour consumption in the study population (p) and the size of the study population (n). Using the conjugate Beta(1,1) prior distribution, the posterior distribution of the parameter p is the Beta ($1 + x, 1 + n - x$) with x representing the number of positive study responses. The beta distribution provides a new wheat flour consumption probability estimate for the binomial distribution for every run in the simulation. In turn, the binomial distribution probability selects if an individual is a wheat flour consumer or not for every iteration in the simulation. The probability estimating the presence of soy in wheat flour is modeled in a similar manner utilizing analytical results from the market survey.

The simulated concentrations of soy were randomly selected from the ELISA analytical results for every consumption event. The dose of soy per consumption event was determined using the concentrations of soy in wheat flour and the amount of wheat flour consumed.

3. Results

3.1. Wheat flour market survey

Soybean residues were found in all forms of wheat flour with 22 of 35 (62.8%) of flours containing detectable soy (Table 1) at concentrations of 3–443 ppm soy flour (1.6–236 ppm soy protein). An average serving size for wheat flour (30 g) would contain 0.05–7.1 mg soy protein. Due to the small sample size for each

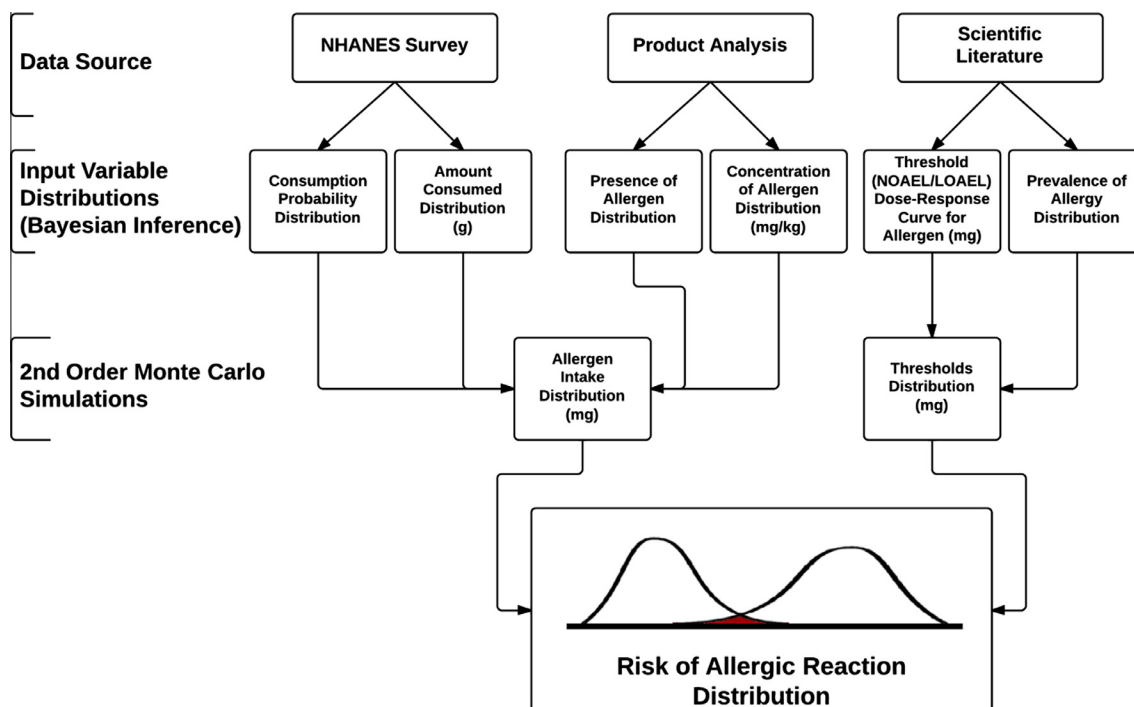


Fig. 1. Probabilistic risk assessment model for food allergens in US products. The general framework of the simulation is a 2nd order Monte Carlo simulation. Distributions of input variables were estimated with a Bayesian inference.

wheat flour category, differences in frequency and levels of soy could not be deemed significant.

3.2. Risk assessment of soy in commercially available wheat flours

On a daily basis, wheat flour is consumed by 97.1% of the total US population, and greater than 99.3% in the population 3 years of age and up (Table 2). Wheat flour has many uses in the US diet. Average wheat flour consumption was 34 ± 36 g or slightly more than a suggested serving of wheat flour per eating occasion. Chocolate chip cookies are consumed by 11.7% of the US population (Table 3). The average chocolate chip cookie consumption amount was 29 ± 29 g (1–2) cookies per day or 5.8 ± 5.8 g wheat flour based on the amount of wheat flour in the chocolate chip cookie recipe.

Simulation risk results are presented as the allergic user risk (Table 4). The allergic user risk assumes every individual is allergic to soybean and consumes wheat flour or chocolate chip cookies. Two simulations were run for wheat flour, first using the range of soy concentrations detected in wheat flour and second with

flour, the predicted number of reactions would be 23.4 ± 4.9 per 100 soy-allergic user eating occasions. The predicted number of allergic reactions from chocolate chip cookies is 6.6 ± 6.9 per 10,000 soy-allergic user eating occasions. No upper or lower limits were set for threshold or consumption estimates and thus as expected, the risk results include predicted reactions occurring at very high consumption levels and among individuals with extremely low threshold doses well outside the original observation range. Thus some of these predicted reactions are not biologically relevant and that must be considered when interpreting the results.

The number of allergic reactions in soy-allergic consumers can be predicted on a per day basis if it is assumed that a soy-allergic individual consumes wheat flour only once per day. The number of eating occasions is found by multiplying the total population, the probability of wheat flour consumption, and the probability that individuals are soy-allergic. In the US, the prevalence of soy allergy is estimated at 0.35% (Sicherer and Sampson, 2010). The minimum number of eating occasions per day by soy-allergic individuals is predicted below:

$$\begin{aligned} \text{Minimum eating occasions per day} &= \text{U.S. population} \times \text{Wheat consumption probability} \times \text{Prevalence of soy allergy} \\ 1.02 \text{ million wheat flour consumption occasions} &= 300 \text{ million} \times 0.971 \times 0.0035 \end{aligned}$$

the maximum amount of 10% soy allowed in wheat by the USDA Grain Inspection Handbook (USDA, 2004). The predicted number of reactions is 2.8 ± 2.0 per 1000 soy-allergic user eating occasions for concentrations of soy found during the wheat flour survey. If the maximal 10% amount of soy allowed was milled into wheat

The number of eating occasions is multiplied by the soy-allergic user risk to predict the number of allergic reactions per day. The number of predicted reactions can be calculated with the equation below:

$$\begin{aligned} \text{Predicted reactions per day from soy in wheat} &= \text{Minimum eating occasions per day} \times \text{Soy-allergic user risk} \\ 2,850 \text{ objective reactions per day} &= 1.02 \text{ million wheat flour consumptions} \times 0.0028 \end{aligned}$$

Table 1
Concentration of soybean in packaged wheat flours^a.

Wheat flours	No. tested	No. positive	Soy protein (ppm ^b)
All purpose flour	13	10	1.6–236
Bread flour	4	2	7.3–152
Pastry flour	3	2	5.0–7.1
White wheat flour	4	2	23–70
Whole wheat flour	10	5	2.1–128
Unique	1	1	39
Total	35	22 (62.8%)	1.6–236

^a Wheat flours were obtained from retail stores in Lincoln, Nebraska, USA.

^b ppm = parts per million (μg per g).

Table 2
Consumption of wheat flour in the United States per eating occasion (defined as 1 h time frame) as determined by the FARE™ program from Exponent®.

Age	Percent user (%)	Mean (g)	Std. Dev. (g)	P90 (g)	Max (g)
Total population	97.1	34	36	73	906
Infants	78.8	14	10	32	167
Children	99.9	28	24	60	446
Teenagers	99.7	42	31	87	906
Adults	99.3	36	44	75	701

Table 3
Consumption of chocolate chip cookies per day in the United States based on the 2003–2006 NHANES database.

Age	Percent user (%)	Mean (g)	Std. Dev. (g)	P90 (g)	Max (g)
Total population	11.7	29	29	56	510
Infants	8.0	14	8	30	71
Children	16.2	26	18	45	126
Teenagers	16.1	29	20	53	315
Adults	9.0	31	40	60	510

Of the predicted reactions, none occurred at doses of soy greater than 88 mg soy protein, the lowest LOAEL found in the 43 DBPCFCs for soy (Magnolfi et al., 1996). From the Log-Normal distribution, the ED₀₅, or dose predicted to provoke a reaction in 5% of the soy-allergic population, is 24.5 mg soy protein with a lower 95% confidence interval of 5.5 mg soy protein; 1.7% of the predicted reactions had doses greater than 24.5 mg soy protein and 41% of predicted reactions had doses greater than 5.5 mg soy protein. The suggested Reference Dose to guide advisory labeling for soy

Table 4
Results of the probabilistic modeling approach to risk assessment of soy in wheat flour due to commodity comingling. Soy-allergic users are assumed to be allergic to soybean and consume wheat flour or chocolate chip cookies. Two simulations were run for wheat flour, first using the range of soy concentrations detected in wheat flour and second with the maximum amount of 10% soy (40,000 ppm soy protein) allowed in wheat by the USDA Grain Inspection Handbook (USDA, 2004).

Product	Consumption pattern	Level of soy present (ppm)	Soy-allergic user risk (%)	Standard deviation
Wheat flour	Total population	1.6–236 ppm soy protein	0.28	0.20
Wheat flour	Total population	40,000 ppm soy protein	23.4	4.9
Chocolate chip cookies	Total population	1.6–236 ppm soy protein	0.066	0.069

flour is 1.0 mg protein in the VITAL program from the Allergy Bureau of Australia and New Zealand (Taylor et al., in press; 83% of predicted reactions had doses greater than 1.0 mg soy protein (Fig. 2A). Due to the large number of available data points in the wheat flour consumption dataset, the Weibull based consumption predictive posterior did not extend beyond the original data points to generate a predicted reaction with an individual threshold greater than 88 mg soy protein. However if the Log-Normal or Log-Logistic statistical distributions are used, biologically irrelevant consumption estimates can be generated at a high enough frequency to predict reactions with an individual threshold greater than 88 mg soy protein (data not shown).

The same methods can be used to calculate predicted allergic reactions per day due to chocolate chip cookie consumption. Chocolate chip cookies were predicted to cause 81 objective allergic reactions per day. No reactions were predicted to occur at doses over 88 mg soy protein, 0% of predicted reactions occurred at doses greater than 24.5 mg soy protein, 1.5% of predicted reactions occurred at doses greater than 5.5 mg soy protein, and 34% of predicted reactions occurred at doses greater than 1.0 mg soy protein (Fig. 2B).

4. Discussion

Detectable levels of soy were found in 62.8% (22/35) of wheat flours during the market survey. All types of wheat flours contained detectable soy proteins. Cake and pastry flours are made from soft wheat due to ideal texture properties imparted by a high starch and low protein content. Soybeans and soft wheat share many growing regions in the US and it could be hypothesized that a higher soy content would be expected in soft wheat flours due to the proximity of soy in the production process. In this survey, the 3 pastry flours contained low levels of soy in comparison to harder wheat flours, but these results could be attributed to the small number of samples. Further studies with larger numbers of samples could be of use to investigate the effects of regional differences on concentrations of soy in different wheat flours and to determine if different types of wheat flours have significantly different levels of detectable soy.

Soy protein was found at concentrations up to 236 ppm in wheat flour, a dose of 7.1 mg soy protein per 30 g serving. No published soy challenges have reported an objective allergic reaction from doses at or below 7.1 mg soy protein. Despite this observation, the quantitative risk assessment indicates that a user risk exists from soy comingling with wheat flour and predicts that 2850 reactions per day will occur among soy-allergic consumers in the US alone. Since no published reports exist of reactions that might be attributable to soy comingling with wheat flour, clinical allergists are either overlooking all of these cases (unlikely if 2850 occur per day in the US) or the quantitative risk assessment is overstating the actual risk. A thorough examination of the inputs to the quantitative risk assessment suggests that several factors could contribute to an overestimation of risk.

The quantitative risk assessment may overstate the actual risk because of the conservatism built into the dose-distribution modeling of individual threshold doses to establish predicted population thresholds. Probably owing to the comparatively low prevalence of soy allergy, published individual threshold data from DBPCFC soy flour challenges were found for only 43 soy-allergic individuals. By comparison, peanut allergy is far more prevalent with a published dataset that contains thresholds from 450 peanut-allergic individuals (Taylor et al., 2010). With this large dataset, the ED₀₅ for peanut can be established with rather narrow 95% confidence intervals. In contrast, the low number of individuals used for dose-distribution modeling of soy thresholds results in

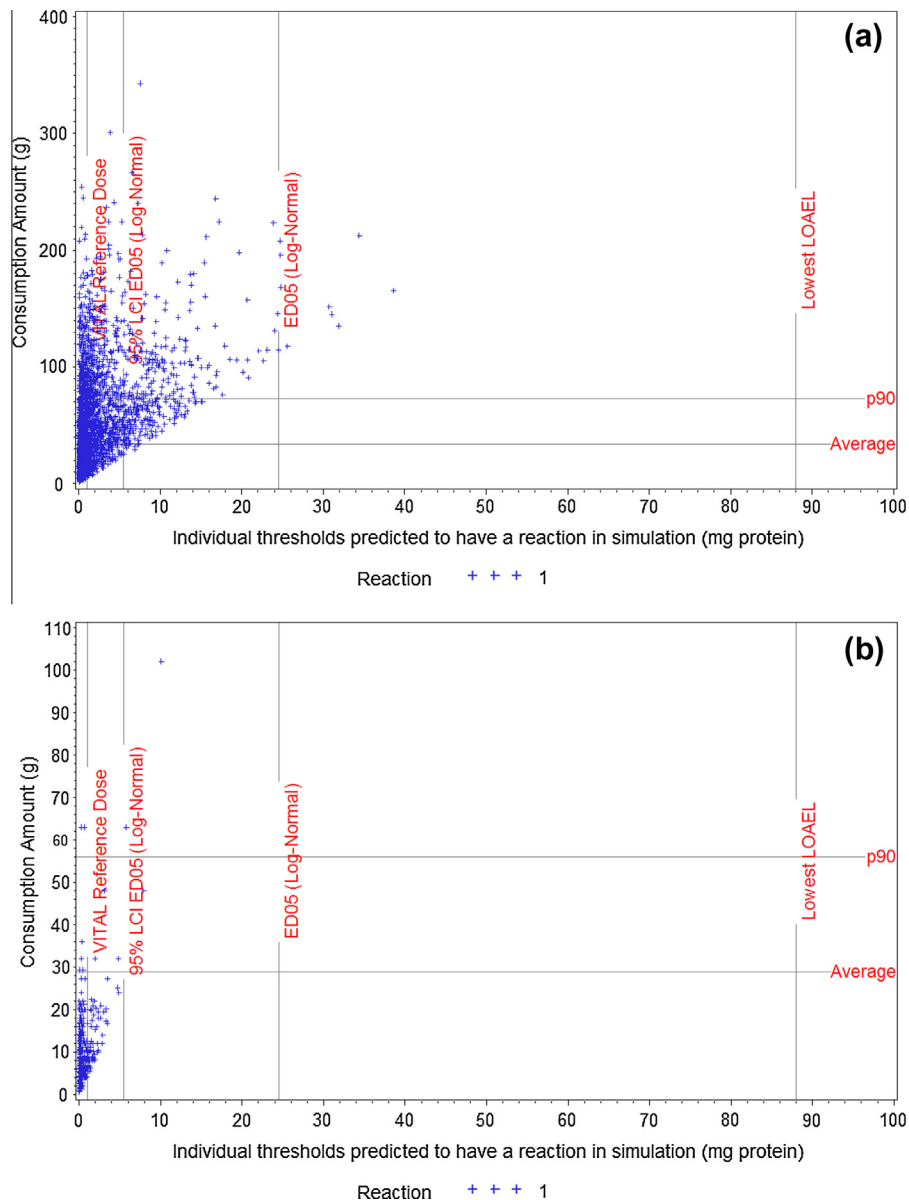


Fig. 2. Thresholds of predicted reactions expressed as mg protein (x-axis) with the predicted consumption (y-axis) for each reaction: (A) soy in wheat simulation and (B) chocolate chip cookie simulation. Each plus symbol represents a predicted allergic reaction during the simulation. The Log-Normal ED_{05} , or the dose predicted to provoke a reaction in 5% of the soy flour-allergic population, and its lower 95% confidence interval are 24.5 mg and 5.5 mg soy protein respectively and labeled where possible. The suggested Reference Dose from the VITAL program to guide advisory labeling for soy flour is 1.0 mg protein (Taylor et al., in preparation). Additionally, the most sensitive individual threshold in the soy dataset is labeled. Relevant consumption estimates are also labeled.

an ED_{05} that is well below the lowest actual observation point with much wider confidence intervals. Probabilistic risk assessment is still an option with fewer subjects, but the predicted threshold distribution will vary widely within the Bayesian context. Additional clinical data from soy challenges would be valuable to increase the statistical confidence in the population threshold estimates. Furthermore, the study populations for three of the studies used (Fiocchi et al., 2003; Magnolfi et al., 1996; Zeiger et al., 1999) involved infants, while the remaining study (Ballmer-Weber et al., 2007) assessed an older patient population. Supplementary data on older children and adults would enrich the current threshold dataset especially because soy-allergic infants and young children often outgrow their soybean allergies (Wood, 2003).

Additional challenges exist regarding the selection of soy-allergic subjects due to the findings that specific challenge materials may have considerable influence on the threshold estimates. For

this project, the selection of soy-allergic subjects was restricted to individuals challenged with soy flour, a minimally processed form of soy that most closely mimics the form of soy that would exist in wheat flour. We are aware of additional challenges conducted with soy milk containing soy protein isolates but the soy proteins in soy protein isolates are more highly processed and modified. Recent unpublished clinical observations from a Dutch clinic indicate that many of the soy milk-allergic patients can tolerate soy flour, suggesting that soy allergy is sometimes associated with certain specific types of soy products. These individuals allergic to soy milk and certain types of soy protein isolate but able to tolerate soy flour seem less relevant for the purposes of risk assessment of soy in wheat flour although this soy-allergic subpopulation merits further studies.

Since the quantitative risk assessment may overstate the actual risk, an evaluation of other approaches to risk assessment was war-

ranted. The most sensitive objective NOAEL found in the clinical literature for soy flour challenges was 83.7 mg soy protein (Ballmer-Weber et al., 2007), while the most sensitive objective LOAEL was 88 mg soy protein (Magnolfi et al., 1996). A NOAEL-based risk assessment would utilize a 10-fold safety factor to convert the LOAEL of 88 mg soy protein to a NOAEL equivalent of 8.8 mg soy protein. If a benchmark dose risk assessment were used, a Reference Dose comparable to the lower 95% confidence interval of the ED₀₅ would be selected from the Log-Normal, Log-Logistic, or Weibull distributions (5.5 mg soy protein using the Log-Normal distribution). A NOAEL-based worst case scenario utilizing the p90 consumption of 73 g wheat flour with a soy protein concentration of 236 ppm contains a dose of 17.2 mg soy protein. The risk of an allergic reaction to the most sensitive soy-allergic individuals could not statistically be ruled out but this dose is 5-fold lower than the lowest LOAEL from challenge studies. Thus, the possibility of allergic reactions from soy in wheat are predicted from such deterministic safety assessment approaches in agreement with probabilistic modeling.

Additional factors also contribute to the overestimation of the risk to soy-allergic consumers due to soy in wheat. The estimated prevalence of soy allergy of 0.35% (Sicherer and Sampson, 2010) is likely too high. Historically, estimates of soy allergy prevalence have been based on perceived allergy or sensitization in pediatric populations (Luccioli et al., 2008; Zuidmeer et al., 2008). An estimated 50% of children will outgrow their soy allergy by the age of 7 (Savage et al., 2010) and up to 70% of all children with food allergies ultimately outgrow the condition (Eggleston, 1987). Thus, the prevalence of soy allergy in the adult population is likely quite low, although not precisely known. Perception of adverse reactions to food far outnumbers the true prevalence of food allergy (Rona et al., 2007; Zuidmeer et al., 2008). Studies estimating the prevalence of soy allergy based on the rate of sensitization to soy through skin prick tests or evidence of soy-specific IgE in patient serum will also overestimate the prevalence of soy allergy since sensitization alone does not equate to true food allergy (Sicherer and Sampson, 2010; Zuidmeer et al., 2008). Individuals with allergies to other legumes including peanut will often have positive skin tests to soy or the presence of soy-reactive IgE in their sera (Bernhisel-Broadbent and Sampson, 1989; Bernhisel-Broadbent et al., 1989). Several studies have shown that fewer than 10% of patients with evidence of soy-specific IgE in their sera will react adversely on blinded oral challenge (Giampietro et al., 1992; Magnolfi et al., 1996). In a study of 1397 unselected Swedish adults, ages 20–44, 2% showed evidence of soy-specific IgE in their sera (Bjornsson et al., 1996). Challenges were not done to confirm soy allergy in that study, but if <10% of individuals with soy-specific IgE have challenge-confirmed soy allergy, then the estimated prevalence of soy allergy in Sweden is <0.2%. Oral challenges found 0.5% of children (4 of 739 responders) up to age 17 were allergic to soy milk (Roehr et al., 2004). However, with soy, the form of soy and degree of processing influence reactivity as some soy patients can tolerate further cooked or processed soy products (Mittag et al., 2004) and others are reactive to soy milk but tolerant to soy flour. All of these factors combined indicate a prevalence of soy allergy in the overall population is <0.2%.

Another factor contributing to the overestimation of risk involves the upper-bound estimates of consumption for wheat flour from the probabilistic simulations. Several of the predicted reactions (4.3%) occurred with individual consumption amounts greater than the 99th percentile estimate for intake at amounts ranging from 150 to 240 g wheat flour (35–58 mg soy protein), equivalent to 5–8 suggested servings of wheat flour in one sitting. No predicted dose for a reaction was above 60 mg soy protein while the lowest observed LOAEL in clinical challenges was 88 mg soy protein. A significant portion of the predicted reactions (32.2%) had

consumption estimates greater than the 90th percentile consumption estimate for wheat flour, 73 g. More realistic consumption amounts of a highly contaminated wheat flour can produce doses of soy protein close to the lower 95% confidence interval of the ED₀₅ from the threshold curve, 41% of predicted reactions had doses greater than 5.5 mg soy protein.

The probabilistic risk assessment of chocolate chip cookies predicts 81 soy-allergic reactions per day due to cross contamination of soy in wheat. The simulation estimates 29 of the 81 reactions occur after consumption of 1 cookie (29 g), the average consumption amount in the US. Additionally, 34 reactions were predicted after consumption of 2 cookies, 8 reactions after consuming 3 cookies, 8 reactions after consuming 4 cookies, and 2 reactions after consumption amounts greater than 4 cookies. However, in reality, few soy-allergic individuals would be likely to react to the levels of soy found in chocolate chip cookies. No reactions were predicted to occur at doses above the ED₀₅ of 24.5 mg soy protein (105 g wheat flour, 18 cookies). Certainly, the predicted 81 daily reactions to chocolate chip cookies have not been observed or reported among soy-allergic consumers. The predicted risk from chocolate chip cookies is likely an overestimate of the actual risk for the same reasons as outlined for overall wheat flour consumption.

While the quantitative risk assessment predicts a level of risk from soy comingling with wheat, that level of risk is small (2.8 ± 2.0 per 1000 soy-allergic user eating occasions for consumption of wheat flour based upon the analysis of wheat flour in our survey), likely overestimated as noted, and not evident from reported clinical observations. In DBPCFC, experienced clinicians are recording relatively mild transitory objective reactions occurring at specific doses; these become the LOAELs. Perhaps some mild reactions are indeed occurring from the consumption of wheat based products by the soy-allergic population but they are so mild and short-lived that affected individuals do not complain or seek medical attention. Additionally, unexplained allergic reactions constitute a substantial number of reported cases and it is possible that some of these reactions are caused by a lack of knowledge that soy exists in wheat flour due to commodity comingling. However, it is our opinion that the vast majority of soy-allergic individuals should not be advised to avoid foods with wheat flour, although the possibility exists that a small number of highly sensitive soy-allergic consumers do exist who could be at risk from such exposures.

However, justification may exist to consider revision of the long-standing USDA grain standards which now allow a maximum of 10% soy in wheat and other commodities. The level of predicted risk (23.4 ± 4.9 per 100 soy-allergic user eating occasions) occurring at that level of soy in wheat flour is 100-fold higher than predicted from our actual analytical survey. Consideration should be given to lowering these allowable levels of soy comingling to assure protection of soy-allergic consumers. From our survey of wheat flour, the milling industry appears able to achieve a much lower level of soy contamination from comingling.

The only strategy to prevent an allergic reaction is avoidance of the food. Current food allergen regulations allow for commodity contamination of agricultural products to go unlabeled. Our conservative risk assessment shows that a few sensitive soy-allergic individuals could have mild, objective reactions after consuming large amounts wheat flour or wheat based products. Clinical reports of allergic reactions attributable to soy contamination of wheat flour do not match with the simulated level of risk, indicating that the risk assessment model is very conservative and that mild reactions, if they are actually occurring, are going unreported. Consequently, the labeling of soy in wheat flour and other wheat-based products is not advocated because it would materially diminish the quality of life for individuals pursuing a soy avoidance diet while no known effect on enhancing their health.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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