August 2, 2006

Food and Drug Administration (FDA)
Office of the Ombudsman
Food and Drug Administration
5600 Fishers Lane
Room 14B03, HF-7
Rockville, MD 20857

Subject: Request for Information Correction per the HHS Information Quality Guidelines

Dear Sir or Madam,

I am writing per the HHS Information Quality Guidelines to request that information be corrected in the following documents:

Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food March 2006. http://www.cfsan.fda.gov/~dms/alrgn2.html (hereafter referred to in my letter as the "thresholds report").

FDA's Responses to Public Comments on the Draft Report "Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food" March 2006. http://www.cfsan.fda.gov/~dms/alrgcom.html ((hereafter referred to in my letter as the "response to comments document").

As the parent of a child with severe food allergies, my family could be substantially affected by the information in these reports. Any thresholds for food allergens that are used based on these recommendations have the potential to have a life-or-death impact on my child. I appreciate the opportunity to participate in this process and ensure that FDA's recommendations on food allergies are based on quality information.

Below are the specific reasons for believing certain information in these two documents is in error, the supporting documentation for this belief and my specific recommendations for correcting the information.

Issue 1: Uncertainty Factor

Section IV.C.1.a of the thresholds report contains the following statement:

"Based on currently available data, the Threshold Working Group was unable to identify any scientifically-based studies that indicate that the standard 10-fold uncertainty factor used in safety assessments for inter-individual variability is not adequate to account for variation within the sensitive population."

However, this statement is directly contradicted by an earlier statement in the very same report found in Section II.F.2:

"Studies have shown that there may be a range of as much as one-million-fold (10^6) in eliciting doses from the least sensitive to the most sensitive individuals (Leung *et al*., 2003; Wensing *et al*., 2002b; Bindslev-Jensen *et al*., 2002)."

Moreover, the misleading implication of this statement (that a 10-fold uncertainty factor is adequate) is also undermined by other findings in the thresholds report:

"Most oral challenge studies are designed to establish a diagnosis of food allergy rather than to determine safety (Taylor *et al*., 2004)." (Section II.F.1) "Because most clinical studies exclude patients who have had previous anaphylactic reactions or who have high specific IgE titers, it is possible that the most sensitive individuals within the allergic population may be systematically excluded from these studies." (Section IV.C.1.a)

In addition, this statement is contradicted by some of the findings of the Food Advisory Committee, who was charged by FDA to review the draft thresholds report. Specifically, according to pages 24 – 25 of the July 15, 2005 transcript found at http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4160t1.doc, several members of the Food Advisory Committee found that:

"IgE-mediated allergic reactions essentially are amplifiers. They amplify reactions to minute amounts of allergens. So, the application of uncertainty factors to thresholds on the double-blind, placebo-controlled, food challenge may not be sufficiently large to handle this variation of amplification of an allergic response."

Finally, I specifically raised this issue of the two contradicting statements on pages 3 -4 of my public comments to the draft thresholds report, found at http://www.fda.gov/ohrms/dockets/dockets/05n0231/05N-0231-EC6-Attach-1.pdf. However, the response to comments document does not address this comment.

Recommendations for Correction:

At minimum, the following statement should be removed from the thresholds report as lacking in both utility and objectivity:

"Based on currently available data, the Threshold Working Group was unable to identify any scientifically-based studies that indicate that the standard 10-fold uncertainty factor used in safety assessments for inter-individual variability is not adequate to account for variation within the sensitive population."

In addition, the above statement should be replaced with something like:

"Based on currently available data on the large range of sensitivities of allergic individuals (i.e., a million-fold) and the likely systematic exclusion of the most sensitive individuals from the clinical data, the standard 10-fold uncertainty factor used in safety assessments for inter-individual variability might not be adequate to account for variation within the sensitive population."

In addition, the response to comment document should be also be revised to include FDA's response to my specific comment that the statement about the reports on the million-fold range of sensitivities contradicts the later finding that the Threshold Working Group was "unable to identify any scientifically-based studies that indicate that a 10-fold uncertainty factor. . .is not adequate."

Issue 2: Data Used to Support the Statutorily-Derived Approach

The discussion in Section IV.C.2.d of the thresholds report regarding the data used for the statutorily-derived approach (which would use the protein levels in highly refined oil to set thresholds for protein in all foods) is deeply flawed and contradicts the consensus findings of the Food Advisory Committee.

First of all, the decision to exclude the four studies that reported allergen levels as "not detected" from Appendix 3 is not transparently explained. There is no discussion at all in the text of the document, and the footnote to the Appendix only states that there was a "lack of methodological information."

However, I doubt that the methodology of these four presumably peer-reviewed studies is any more lacking than that of the other studies. Although I was unable to examine the source materials themselves, an earlier discussion of the studies in another context in the thresholds report included the detection sensitivities, which argues that there was some methodological information.

On the other hand, for the studies with positive values that were included, the footnote to Appendix 3 states: "None of the publications provide sufficient information to evaluate the overall extraction efficiency, accuracy, reproducibility, or precision of the method used. In addition, in most cases, it was not clear whether replicate samples were tested or whether replicate measurements were carried out for individual samples."

In other words, if "lack of methodological information" was an adequate reason to exclude data, then ALL the data should have been excluded. Choosing to only exclude the non-detects is an unacceptable bias, particular when the Appendix 3 levels are used in

the text to calculate mean concentrations and standard deviations for hypothetical threshold levels.

In fact, given the Food Advisory Committee's report, it is clear that using any of the data to calculate even hypothetical thresholds is irresponsible. The Food Advisory Committee's findings are unambiguous:

"There was consensus that the levels in protein in oils did not apply to all food allergens for the following reasons: (1) the accuracy of the methods used to measure protein in oils is poor or undefined, (2) denaturation and changes in the structures of allergenic conformational epitomes may alter whether or not there is an allergic reaction to the protein in oils (3) studies indicated that the matrix effect (fat levels) can affect does level needed for an adverse response." (July 13-15, 2005 Summary Minutes, p. 8) http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4160m1_summary%20minutes.pdf

However, in the limitations section of the thresholds report discussion of this issue, there is no mention of these three serious limitations. The limitations section does mention a "lack of data" but does not discuss the poor quality of the existing data. The other limitations raised by the Food Allergy Committee are not discussed at all.

This omission is particularly distressing because this section of the thresholds report also includes the erroneous statement:

"Based on the data that are currently available and estimates of the amount of oil consumed as a food or food ingredient, it is likely that a threshold based on this approach would be unnecessarily protective of public health."

NOTHING in the currently available data would make one conclude that the levels in oil would be "unnecessarily protective of public health." In fact, the later two points that the Food Allergy Committee raised (denaturation and matrix effects) would lead to the conclusion that the oil levels would NOT be protective (see July 13, 2005 transcript, pages 408-410)

Recommendations for Correction:

In order to ensure the utility and objectivity of the information used in this report, I recommend the following corrections:

Either (1) add the data on non-detects of protein in oils to Appendix 3, or (2) delete Appendix 3 entirely, or (3) add a transparent explanation to the text of what was lacking in the methodology of the four reports with non-detects that was not also lacking in the reports with detectable protein.

Delete the paragraph in Section IV.C.2.d discussing threshold value calculations. Calculating the mean and standard deviation based on the poor quality data in Appendix

3 gives a false sense of confidence to data that have been found inutile by the Food Advisory Committee.

Add to the discussion of the limitations in Section IV.C.2.d the limitations that were identified in the Food Advisory Committee report, namely: (1) the accuracy of the methods used to measure protein in oils is poor or undefined, (2) denaturation and changes in the structures of allergenic conformational epitomes may alter whether or not there is an allergic reaction to the protein in oils and (3) studies indicated that the matrix effect (fat levels) can affect does level needed for an adverse response."

Most importantly, delete ALL references to the unsupported statement that current data indicate that the levels in the statutory-based threshold are "unnecessarily protective of public health," including (and especially) the use of this statement in all discussions of Finding 5 of the report.

Finally, the response to comments document should be updated to reflect whichever changes that are made regarding the inclusion of data on non-detects in Appendix 3.

Thank you again for your consideration of my request. If you have any questions, please don't hesitate to contact me.

Sincerely,