DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

JUL 31 2007

Alexandria, Virginia

Dear Ms. :

This letter is in response to your letter of January 15, 2007, requesting, pursuant to the U.S. Department of Health and Human Services Guidelines for Ensuring the Quality of Information Disseminated to the Public,[1] that the Food and Drug Administration (FDA) reconsider its response to your "request for correction" (RFC) concerning two FDA documents:

1) Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food (March 2006) (referred to herein as the "Threshold Report")[2]; and

2) FDA's Responses to Public Comments on the Draft Threshold Report (referred to herein as the "Public Comments Report").[3]

In your letter, referred to herein as the "request for reconsideration" (RFR), you ask for reconsideration of Dr. Robert Buchanan's December 15, 2006 response to your request for correction, dated August 2, 2006.

You allege that FDA's response is inadequate for 5 specific reasons. I have renumbered them here because there are two items numbered "2" in your letter. Your summary paragraphs for each assertion are reproduced in full below.

1. **"FDA's assertion that 'the purpose of Threshold Report was not to decide whether to establish any thresholds for allergens, to prescribe the use of any specific approach if a decision were made to establish any such thresholds, or to suggest any specific threshold value' is inadequate to prevent misuse of the faulty information in the report."**

You express concern that the report will be improperly cited in the future: "Secondary references will quote the findings without the caveats, and tertiary references may not even include the original citation." As you recognize in your letter, the Threshold Report

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[1] The section of the guidelines specific to FDA is available at http://aspe.hhs.gov/infoquality/Guidelines/fda.shtml.

[2] http://www.cfsan.fda.gov/~acrobat/alrgn2.pdf. The document is also available in an html format at http://www.cfsan.fda.gov/~dms/alrgn2.html. Page references in this letter are to the pdf version.

[3] http://www.cfsan.fda.gov/~dms/alrgcom.html. This document was also posted on May 25, 2006. This document represents a summary of the public comments received at the Food Advisory Committee meeting and in the public docket with a brief indication as to how the revised Report responds to each comment.

contains careful discussion of caveats about the uncertainty of the data. Unfortunately, FDA cannot control whether people will misrepresent or mischaracterize the contents of the Threshold Report except by carefully noting the data gaps and limitations, as has been done. While we share your concern, we cannot let the fear of misuse prevent us from portraying the state of the science, including its associated uncertainties, and we strive to have our documents present information as transparently and accurately as possible.

In your RFR, you raise the issue of whether, for the purposes of labeling, subjective symptoms such as nausea and dizziness should be considered an adverse effect. In your RFR, you contend not that the Threshold Report needs correcting, but that it was improperly cited as support for a statement in an FDA guidance document on soy lecithin.[4] I note that a statement in a guidance document is not "a final decision" by the agency, as your letter asserts. Rather, as stated on the face of the guidance, a guidance "represents the current thinking" of the agency on a particular topic. Comments and suggestions on the guidance may be submitted at any time to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with Docket No. 2006D-0169. Additionally, I will ensure that a copy of your letter is provided to the appropriate FDA staff working on the soy lecithin guidance.

As to your contention that information in the Threshold Report is faulty, I disagree that information in the report is faulty for the reasons cited in Dr. Buchanan's response and discussed further below.

2. "FDA's responses to my concerns about a specific statement on the uncertainty factor do not address the central issue."

Your RFR challenges Dr. Buchanan's response to your request that FDA correct the sentence from Section IV.C.1.a of the Threshold Report [page 48]:

> 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 the RFR, you reiterate your concern by stating that you find the sentence above to be "untrue," and point to three studies on inter-individual variability that the Threshold Working Group identified and discussed. You state: [I]n their response FDA has failed to directly address the fact that there is scientific evidence that, based on currently available data, the standard 10-fold uncertainty factor for inter-individual variability may not be adequate to account for variation within the sensitivity allergic population." (Emphasis in original.) You state that "[i]t is important to note that I am not claiming that

[4] "Guidance on the Labeling of Certain Uses of Lecithin Derived from Soy Under Section 403(w) of the Federal Food, Drug, and Cosmetic Act," April 2006, 71 Federal Register 25844 (May 2, 2006).

the 10-fold assumption is clearly inadequate, just that the currently available scientific data indicate that it may be inadequate."

As noted, the studies you reference with respect to this point were considered and discussed by the Threshold Working Group. In particular, they are discussed in detail in section II.F (at p.21) where the Threshold Report describes challenge studies with different populations, different allergenic foods, and different study designs and states that these studies indicate that there is a range in individual sensitivities within the tested populations.

However, the statement you are challenging is not about whether there are studies indicating that there is inter-individual variability within the tested population. Rather, the sentence concerns whether there are studies that indicate that the standard factor used to account for uncertainties in the data concerning this inter-individual variability should be greater than 10-fold. As the Working Group explained in Section IV.B.2 of the Threshold Report (at p.46): "Uncertainty reflects incomplete knowledge about a system or population which can be reduced with additional study. Variability reflects the fact that all systems or populations have inherent, biological heterogeneity that is not reducible through further measurement or study [citation omitted]."

Page 54 of the Threshold Report, which describes sources of uncertainty, reiterates the point that for "intraspecies differences" (i.e., inter-individual variability), "[s]afety assessments typically apply a 10-fold uncertainty factor to account for the variability both between individuals and variability in responses for a particular individual." However, the Report states (at p.55) that "[a]dditional uncertainty factors could be added if justified from data gaps." In particular, the Threshold Report noted that an additional safety factor may be warranted for sensitive subpopulations of individuals, because this is also a source of uncertainty. While some scientists treat this uncertainty as encompassed by the uncertainty concerning inter-individual variability, in the Threshold Report the Working Group identified it as a separate uncertainty factor, if the safety assessment-based approach were used:

> Sensitive population of interest. The existence and size of highly sensitive subpopulations of allergenic individuals and their lack of participation in reported clinical trials is a potential data gap and should be included in the uncertainty factors. It is unclear whether the standard 10-fold uncertainty factor for variability within a species is sufficient to account for potential highly sensitive subpopulations. Because of the potential severity of reaction for this subpopulation, it seems prudent to include an additional margin of safety (e.g., a 10-fold uncertainty factor) for this uncertainty.

(Threshold Report at pp.54-55; emphasis added.) This point is also addressed in Table IV-6 of the Threshold Report (at p.5), which makes clear that uncertainty factors are multiplicative.

I also note that the sentence immediately following the sentence you are challenging (at p.48) states that the assumption that the standard 10-fold uncertainty factor used in safety assessments for inter-individual variability is adequate "should be reexamined as more data on the distribution of sensitivities within the population become available," because of the limitations in the clinical studies and case reports described in the Threshold Report.

3. "FDA's decision to selectively discard data on non-detects is inexcusable."

In your RFR, you question why the Working Group excluded from the calculations described at page 57 of the Threshold Report data from four studies in which there was no information available to support an estimate of value for reported "non-detects." You suggest that it would be appropriate to treat these non-detects as values at half of the detection limit for the method used. Although this approach can be applied when analytical methods have been adequately characterized, it is not possible to do so with respect to these data because none of the publications involved contained sufficient information to determine the detection limits. Because we do not know the detection level in some of these studies, we cannot infer what half the non-detect level would be, and as a result we stand by our decision to exclude these data.

Your RFR suggests that all data from a study are "inutile" if there is insufficient information upon which to estimate a detection limit for some of the reported data. I do not agree. In such a situation, the incomplete data and any analysis based on them would need to be carefully qualified, as was done by the Working Group in the Threshold Report. That careful qualification enables a reader of the Threshold Report to reproduce the calculation reported at the bottom of page 57, where it clearly indicates that, "Based on the data presented *in those studies that reported levels other than 'not detected,'* the overall range of protein concentrations for highly refined oils was 0.014 to 16.7 ug protein/ml oil..." (emphasis added). In addition, Appendix 3 provides all of the information necessary for others to carry out alternate calculations. I note, however, that the lack of validated methods for measuring levels of protein in highly refined oils supports the conclusion of the Threshold Report that the statutorily-derived approach is at best an interim approach.

4. "FDA incorrectly asserts that the Thresholds Reports discussion on a "lack of data" on oils for the statutory approach encompasses the data issues identified by the FAC."

In your RFC, you requested that FDA add to Section IV.C.2.d (at pp. 57-58) a discussion of specific data limitations identified in the FAC summary report at page 8. There, the FAC noted:

> There was consensus that the levels of protein in oils did not apply to all food allergens for the following reasons: (1) the accuracy of the methods used to measure proteins in oils is poor or undefined, (2) denaturation and changes in the structure of allergenic conformational epitopes may alter whether or not there is an allergic reaction to the proteins in oils [; and] (3) studies indicate that the matrix effect (fat levels) can affect the dose level needed for an adverse response.

Dr. Buchanan's response to your RFC states that there is no need to add this specific discussion to the Threshold Report because 1) the phrase "lack of data" encompasses the data issues described in the FAC summary report, and 2) "[m]ore importantly, those comments pertain to issues that would need to be addressed if the statutorily-derived approach were to be applied, but they are not directly related to the description of the strengths, weaknesses, and data needs of that approach, which is the primary focus of this section of the Threshold Report." Dr. Buchanan noted in his response (at p.7) that "[t]he FAC did not question the inclusion of the statutorily-derived approach among the possible approaches that could be used to establish thresholds for major allergens and gluten in food and did not identify any alternative approaches beyond those set out in the Threshold Report."

Your RFR rejects Dr. Buchanan's response. You argue that neither of the limitations noted by the FAC (denaturation and changes in the conformational epitopes, and the matrix effect (fat levels)) has anything to do with lack of data. Rather, you argue that these limitations speak "to inherent limitations of extrapolating protein levels in oil to protein levels in other food."

I agree with Dr. Buchanan that detailed discussion of these issues raised by the FAC is not necessary. While these issues may have some bearing on determining threshold and dose-response, the data on them are so uncertain that at this point no clear statement can be made about the impact of denaturation or the matrix effect on allergenicity. More importantly, I note that this text at page 58 is summary text. The "processing and matrix effects" are discussed more fully in the Threshold Report (at page 52) in a separate section (f) within the section on "evaluation of data availability and data quality," and in even greater detail at pages 25-28.

You also state that you "believe that ...the specific reasons behind the FAC finding should be documented in the report and not hidden behind a discussion of a 'lack of data'." As noted, the Threshold Report did discuss processing and matrix effects length. This discussion was referenced in the question posed to the FAC which resulted in the FAC paragraph statement quoted above. Because technical analysis of data gaps is an activity that takes place within the context of application of a specific approach to a specific allergen, any further discussion is beyond the scope of the Threshold Report.

5. **"FDA's defense of the Thresholds Report finding that the statutory approach might yield thresholds that are "unnecessarily protective of public health" does not address the fact that the limitations identified by FAC would lead to the opposite conclusion."**

The challenged sentence in the Threshold Report at page 58 is as follows:

> 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."

The sentence appears in a discussion of the feasibility of setting a threshold using a statutorily-derived approach. In your RFR, you refer to the challenged sentence as a "major finding" that cannot be made absent a determination that "all scientific information pointed to those thresholds being overly protective." You request that all references to this sentence be deleted.

I agree with Dr. Buchanan that you have taken this sentence out of context. In the very next paragraph, which is a more comprehensive summary paragraph concerning this discussion (Finding 5), the report states:

> This [statutorily-derived] approach might yield thresholds that are unnecessarily protective of public health compared to thresholds established using the safety assessment-based approach or the risk assessment-based approach. However, confirming this would require additional data. If this approach is employed to establish thresholds, it should be used only on an interim basis and should be reevaluated as new knowledge, data, and risk assessment tools become available.

This paragraph is accurate, both with respect to using threshold data from a single food allergen for other allergens (the FAC's third numbered point) and with respect to using data on the level of protein in highly refined oils as a basis for establishing a threshold for other foods containing the same allergen (the FAC's fourth numbered point). In your RFR, you argue that the limitations noted by the FAC—denaturation and matrix effects—could lead "to the opposite conclusion." However, the FAC summary raises these issues but makes clear that data gaps preclude assuming, as your RFR does, that the missing data would lead to lower threshold or dose-response relationships.

CONCLUSION

In summary, after review of your request for reconsideration, I find that neither the Threshold Report nor the Public Comments report requires any corrective action. I appreciate your interest in this matter and the comments you provided during the public meeting and in your RFC and RFR.

Sincerely,

/s/

Robert E. Brackett, PhD
Director
Center for Food Safety
and Applied Nutrition