



DEC 15 2006

Dear Ms.

This letter is in response to your request of August 2, 2006, pursuant to the U.S. Department of Health and Human Services Guidelines for Ensuring the Quality of Information Disseminated to the Public,¹ that we make certain corrections to two 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

These documents are described in the next section, following which I respond to your specific requests for correction. As discussed more fully below, I do not believe that any correction to these documents is warranted.

BACKGROUND

A working group of the Food and Drug Administration (FDA) prepared the Threshold Report to summarize the current state of scientific knowledge regarding food allergies and celiac disease; identify all approaches that could be used to establish thresholds; and evaluate the strengths, limitations, and data needs of each approach. The Threshold Report was not intended to determine whether to establish thresholds for any allergens, to prescribe the use of a specific approach if a decision were to be made to establish any such thresholds, or to suggest any specific threshold values. (As the Threshold Report noted, an option implicit in the Threshold Report is "a decision not to establish thresholds at this time" for food allergens (Section IV.B) (p.45).) Rather, the Threshold Report was intended to be descriptive of the strengths and limitations of the evaluated approaches, and the criteria for evaluation of data availability and data quality. In addition, as stated

¹ The section of the guidelines specific to FDA is available at <http://aspc.hhs.gov/infoquality/Guidelines/fda.shtml>.

² <http://www.cfsan.fda.gov/~dms/alrgn2.html>.

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.

in the Threshold Report (in Section IV.B, at p. 45⁴), “any decisions on approaches for establishing thresholds for food allergens or for gluten would require consideration of additional factors not covered in the current report,” such as legal authority, stakeholder concerns, trade issues, and compliance and enforcement issues.

In June 2005, the draft Threshold Report was published on the FDA website and its availability was announced in the Federal Register.⁵ FDA solicited and received comments and scientific information concerning the draft through an agency docket. In addition, FDA's Food Advisory Committee (FAC) held a public meeting in July 2005 to evaluate the draft Threshold Report; at this public meeting, expert and public comments were submitted to the docket.⁶ On May 25, 2006, FDA posted at its website the two documents that are the subject of your request for correction.

The Threshold Report identifies and analyzes four general approaches that could be used to establish thresholds for allergens: analytical methods-based; safety assessment-based; risk assessment-based; and statutorily-derived. Your request for correction concerns only two of these approaches—the safety assessment-based approach, and the statutorily-derived approach. Briefly, a safety assessment-based approach would be similar to the way in which FDA currently evaluates the safety of food additives. Where a biological threshold can be justified scientifically, a calculation can be made to identify a “safe” level of exposure to a chemical or other substance that takes into account what is known from toxicological, animal, and human studies. Your request for correction focuses on an aspect of a safety assessment known as the “uncertainty factor,” which is a variable in the calculation that accounts for inter-species and inter-individual differences and for data uncertainties. See Threshold Report at IV.A.2, pages 42-43. There are no precise formulas for determining the uncertainty factor to be used in a particular safety assessment.

Under the statutorily-derived approach, a threshold would be established by extrapolating from an exemption set by Congress for another purpose. For example, section 201(qq) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(qq), defines “major food allergen” to include a food ingredient “that contains protein derived” from one of eight identified allergenic foods or food groups, “except...any highly refined oil” derived from one of those foods. Thus, in theory a threshold could be established for all food allergen proteins based on the level of protein in highly refined oils, since Congress has made such oils exempt.

Your request for correction does not challenge the overall soundness of the evaluation of these approaches reflected in the Threshold Report, but rather challenges specific statements in the report with respect to the data discussed in the sections concerning these

⁴ All references to the Threshold Report provide both the section and the page number from the printed Report. Page numbers may differ if the Report is accessed in other formats.

⁵ See notice of availability, 70 FR 35258 (June 17, 2005).

⁶ A transcript of the meeting is available at <http://www.fda.gov/ohrms/dockets/ac/cfsan05.html>. The Committee's answers to specific scientific questions is available in a summary report at http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4160m1_summary%20minutes.pdf.

two approaches. As indicated in your request for correction, your primary concern is the potential effect on the health of your family if a threshold for allergens were to be established using the approaches recommended in the Threshold Report. I hope this background information helps to clarify that the purpose of the 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 values.

REQUEST FOR CORRECTION AND RESPONSE

Your request for correction raises two issues and recommends certain corrections. For ease of reading I have numbered specific points and signaled which paragraphs set forth my responses.

The Uncertainty Factor in the Safety Assessment-Based Approach

Your letter challenges the following 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.

You assert that this statement lacks utility and objectivity and request that it be removed and replaced. You base this request on three assertions, which are described and responded to in order.

1. You assert that the sentence on page 48 is “directly contradicted” by an earlier sentence in Section II.F.2 [page 23]: “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).”

Response: First, it may be helpful to read the text immediately following the sentence you quote from Section IV.C. 1. It reads:

However, because of the limitations in the clinical studies and the case reports discussed above, this assumption should be reexamined as more data on the distribution of sensitivities within the population becomes available.

As this sentence at p. 48 notes, the Working Group specifically recommended reevaluation of the assumption that a standard 10-fold uncertainty factor for inter-individual variability is adequate as more data become available. It is also helpful to note that other sources of uncertainty—such as limitations in clinical data or the need to extrapolate from animal research—could also add multipliers to the final Uncertainty

Factor used in establishing a threshold if the safety assessment-based approach were to be used.

In addition, the discussion in Section IV.B.2 (page 47) states: “A minimum uncertainty factor of 10 is generally used to account for variation within the population when relying on human data and additional uncertainty factors may be included as appropriate” (emphasis added).

2. You allege that the “misleading implication of this statement (that a 10-fold uncertainty factor is adequate) is also undermined by other findings in the threshold 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 (page 22)); and “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 [page 47]).

Response: These two quoted sentences support the finding in the Threshold Report that there are limitations to the clinical studies. As discussed in the preceding response, these limitations would be taken into consideration when determining an appropriate Uncertainty Factor if the safety assessment-based approach were to be applied. As stated above, if a safety assessment-based approach were to be used, additional uncertainty factors will be considered as appropriate.

3. You allege that the sentence is contradicted by some of the findings of the FAC (July 15, 2005 transcript at pps. 24-25), as follows:

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.

Response: This statement by an FAC member during discussion is consistent with the Threshold Report and the sentence you challenge in your letter. In addressing the issue of appropriate uncertainty factors, the same FAC member also said (see transcript at 22-23):

- “The uncertainty factor for sensitive populations is unknown...”
- “The selection of an uncertainty factor for allergens should be informed by the distribution of the NOAELs and the LOAELs...”
- “If reproducible, subjective responses in patients with a history of life-threatening anaphylaxis are included in setting LOAELs and NOAELs, the uncertainty factor might be lower than 10.”

In sum, I do not agree that the challenged sentence should be removed because it lacks objectivity or utility. The point made in the challenged sentence is supported by the

surrounding discussion. The Threshold Report discusses complex scientific issues, methods, and data. Because of the complexity of the subject and the evaluative nature of the text, it is important that individual sentences and any interpretation of the text and its findings be considered within the context of the full Report. As indicated in the Threshold Report, the Uncertainty Factor that would be used if the safety assessment-based approach were to be applied would be determined on the basis of the data available at that time and would consider the limitations of those data. In context, the challenged statement is both objective and useful to the reader.

4. You allege that FDA's Public Comments Report does not respond to essentially this same comment made by you in your written comments concerning the draft Threshold Report.⁷ You request that the Public Comments Report be revised to include FDA's response to your specific comment.

Response: I do not agree that the Public Comments Report needs to be revised because your comments on this point were addressed there, as reflected in this line pulled from the summary comment table below. If a safety assessment-based approach is used, the available data will be used to inform decisions on the uncertainty factors.

Topic Area	Commenter	Summary of Comment	Response
Safety assessment-based approach	Individual Consumer	The currently available clinical data deliberately exclude the populations that are most likely to be of concern. There is no scientific evidence that a 10-fold uncertainty factor would be protective.	This issue is discussed in the report and the Committee's comments. If the safety assessment-based approach is implemented, decisions on uncertainty factors will be based on the available data.

Data that Might Be Used in Applying the Statutorily-Derived Approach

You assert that “[t]he 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.” You further assert that “using any of the data to calculate even hypothetical thresholds is irresponsible.” Your request for correction raises a number of specific concerns, addressed below in the order in which your letter discusses them.

5. You allege that “the decision to exclude the four studies that reported allergen levels as ‘not detected’ from Appendix 3 is not transparently explained.” You note that a footnote to the appendix states that there was a “lack of methodological information,” but state that you doubt that the methodology for these studies was any more lacking than

⁷ <http://www.fda.gov/ohrms/dockets/dockets/05n0231/05N-0231-EC6-Attach-1.pdf>.

footnote to the appendix states that there was a “lack of methodological information,” but state that you doubt that the methodology for these studies was any more lacking than that of the other studies. You acknowledge that you did not examine these source materials, but state that “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.” You indicate that if the reason to exclude data is “lack of methodological information,” then all of the data should have been excluded, and that exclusion only of the “non-detects” reflects an unacceptable bias.

Response: The footnote in Appendix 3 (page 102) reads as follows:

“Protein levels too low to detect or measure were reported by Tattrie and Yaguchi (1973), Hoffman and Collins-Williams (1994), Yeung and Collins (1996), Peeters *et al.* (2004) for peanut oils and by Tattrie and Yaguchi (1973), Porras *et al.* (1985) for soy oils. These values were not included due to the lack of methodological information.”

Some, but not all, data from five, not four, studies were excluded from the calculations described on page 57, because, as stated in the footnote to the table, those samples were reported to contain undetectable levels of such proteins. Because the published descriptions of these studies did not contain the information needed to determine the meaning of “undetectable,” we decided not to include those data in the table. We were careful to explain that decision in the Threshold Report at p. 102 (footnote). Furthermore, sufficient data were provided to allow anyone to reproduce our calculations or to use the data in alternative calculations. The criteria for evaluating the analytical methods for protein in oil studies are described in Table IV-7 at p. 57.

In the footnote quoted above, the Working Group did not indicate that these studies had methodological limitations reflecting on the study’s reliability or validity, as your request for correction suggests. Rather, the footnote indicates that particular values were excluded because we were not able to estimate them. Indeed, some data from three of the five studies were reported in Appendix 3. A finding that protein was not detected does not necessarily indicate that it was absent; rather it indicates that it may have been present at a level too low to be detected by the method used. In these tests, overall sensitivity may be affected by a large number of factors, including extraction efficiency and the potential presence of interfering substance.

To correct this alleged bias, you request that we add the data on non-detects of protein in oils to Appendix 3, delete the Appendix entirely, or add a transparent explanation to the text of what was lacking in the methodology of the reports with non-detects that was not also lacking in the reports with the detectable protein. As this discussion indicates, no correction is needed. Citations for those studies that reported non-detection are provided in the footnote to Appendix 3 quoted above.

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 (3) studies indicate that the matrix effect (fat levels) can affect the dose level needed for an adverse response.

You further assert that the “poor quality of the existing data” is not discussed in the section of the Threshold Report that describes data limitations (although, as you acknowledge, it does identify and discuss a “lack of data”).

In light of these concerns, you request that FDA add to Section IV.C.2.d [pps. 57-58] a discussion of the specific data limitations identified in the FAC summary report.

Response: I disagree that the discussion of the statutorily derived approach needs to be revised. The Threshold Report at IV.C.2.d includes an objective and transparent evaluation of the available data and the limitations of those data. The criteria for evaluating published studies that measured protein concentration in oils were explained in Table IV-7 (page 57) and applied in the Appendix 3 table. The data and information in Appendix 3 were then summarized in the report on page 57. It is clear from the Threshold Report that these data are very limited, both in the number of studies available and in the nature of the information they provide. It is also clear from the Threshold Report that the purpose of the summary of data in the section that describes the statutorily-derived approach was to illustrate the range of values that had been reported in the literature and to provide scientific context for the discussion of the advantages and limitations of that approach. The Threshold Report at IV.C.2.d is transparent in acknowledging the limitations of the available data. The calculations are clearly for illustrative purposes only, not for establishing threshold levels.

With respect specifically to the comments in the FAC summary report, I do not believe that there is any reason to add that discussion to the Threshold Report. First, the phrase “lack of data” encompasses the data issues described in the FAC summary report. More 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. The 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.

7. You allege that the data do not support the following sentence in the Threshold Report, and that the sentence is erroneous: “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.” You request that all references to this sentence be deleted.

Response: This sentence on p. 58, which is at the end of the discussion of the limitations of the statutorily-derived approach, is taken out of context. In the very next paragraph, which is a more comprehensive summary paragraph (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 wording makes clear that this is only a possibility and provides a comparative context.

I also note that the FAC summary report also suggests that the use of threshold data for a single allergen to establish thresholds for other allergens might prove too restrictive. At page 8, the FAC summary report states: "The Committee also expressed concern that labeling based on threshold data from a single food could unnecessarily restrict diets for consumers and pose hardships to industry."

8. You maintain that "[c]alculating 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." You request that FDA delete the paragraph in Section IV.C.2.d [p. 57] discussing threshold value calculations.

I do not believe that there is any reason to delete the paragraph in Section IV.C.2 discussing threshold value calculations. The Working Group appropriately characterized the limitations of the data and the very conditional and hypothetical nature of this calculation. I also disagree that the FAC found these data inutile. Discussing the data and using them to illustrate the statutorily-derived approach enhanced the utility of the Threshold Report in communicating the strengths and weaknesses of one of several approaches to establish thresholds for allergens. The FAC found that the available data indicate that the levels in protein in oils are not applicable to all food allergens for a range of reasons; this does not mean those data are not useful to illustrate how a calculation might be approached, which is what the Threshold Report does.

CONCLUSION

In summary, after review of your request for correction, I do not find that the Threshold Report or the Public Comments Report require any corrective action. I appreciate your interest in this matter and the comments you provided during the public meeting and in your request for correction.

You may submit a written or electronic request for reconsideration within 30 days of receipt of this response. The request for reconsideration must state the reasons that you believe this response to be inadequate. You must attach a copy of your original request

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