

Food Advisory Committee Meeting
July 13-15, 2005
Advice on CFSAN's Draft Report:
Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food

Executive Summary

On July 13-15, 2005, the Center for Food Safety and Applied Nutrition (CFSAN) convened a meeting of the external Food Advisory Committee (henceforth, "Committee.") to evaluate CFSAN's draft report, "Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food." (henceforth, "Report.") The Committee heard presentations on the symptoms and diagnosis of food allergy, the quality of life issues faced by patients and their families, the reliability and availability of analytical test methods, the design and conduct of oral challenge studies, and the use of data to model dose-response distributions. The Committee also heard presentations on the diagnosis and treatment of Celiac disease, the quality of life issues faced by patients and their families, the relationship between gluten proteins in various grains and Celiac disease, analytical methods for measuring gluten levels in food, the value and use of prospective and retrospective studies, and a summary of existing national and international definitions of "gluten-free" standards for food labeling. Members of the public representing trade associations, industry, consumers, and other stakeholders also presented comments to the committee.

The presentations, public comments, Committee discussions, and the Committee responses to questions posed by CFSAN are recorded in the transcript of the meeting. A summary of the Committee responses to the questions is also provided in the Summary Minutes.

The Committee concluded that CFSAN's Draft Report includes a comprehensive evaluation of the currently available data and descriptions of all relevant approaches that could be used to establish thresholds for major allergens and gluten in food. The Committee suggested that, while the safety assessment-based and risk assessment-based approaches are distinct, they are not mutually exclusive. For example, statistical analyses could be incorporated into a traditional safety assessment by considering dose-response distributions. The Committee felt that the risk-assessment-based approach is scientifically the strongest of the approaches, and that it should be used in a transparent manner with appropriate consideration of data uncertainties, when sufficient data become available. The Committee agreed that the criteria identified in the Report for evaluating the available data were appropriate. The Committee noted that a technology assessment prepared for the Agency for Healthcare Research and Quality identified a similar set of criteria for evaluating published clinical data. The committee also recommended that data from highly-relevant, well-designed studies be considered in establishing thresholds, even if they have not yet been published or peer-reviewed.

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Summary Minutes

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FOOD ADVISORY COMMITTEE MEETING

Advice on CFSAN'S Draft Report:

Approaches to Establish Thresholds
for Major Food Allergens and for Gluten in Food

Wednesday, July 13, 2005 thru Friday, July 15, 2005

Greenbelt Marriott
6400 Ivy Lane
Grand Ballroom
Greenbelt, Maryland 20770

PARTICIPANTS

FOOD ADVISORY COMMITTEE STANDING MEMBERS:

Richard A. Durst, Ph.D. - Acting Chairman
Jeffrey A. Barach, Ph.D. (Industry Representative)
Patrick S. Callery, Ph.D.
Dennis Gonsalves, Ph.D., M.S.
Jean M. Halloran (Consumer Representative)
Douglas C. Heimbürger, M.D., M.S.
Margaret C. McBride, M.D.
Mark Nelson, Ph.D. (Industry Representative)
Carol I. Waslien Ghazai, Ph.D., R.D.

TEMPORARY VOTING MEMBERS:

Petr Bocek, M.D., Ph.D.
Margaret Briley, Ph.D., R.D.
Erica Brittain, Ph.D.
Ciaran P. Kelly, M.D.
Soheila June Maleki, Ph.D.
David O. Oryang
Marc D. Silverstein, M.D.
Suzanne Teuber, M.D.

FOOD AND DRUG ADMINISTRATION:

Robert Brackett, Ph.D.
Catherine Copp, J.D.
Steven M. Gendel, Ph.D.
Rhonda R. Kane, M.D., R.D.
Michael M. Landa, J.D.
Stefano Luccioli, M.D.

FOOD AND DRUG ADMINISTRATION STAFF:

Marcia Moore, Food Advisory Committee Staff
Jenny Slaughter, FDA Ethics Staff

GUEST SPEAKERS (July 13, 2005):

Catherine Copp, J.D.
Rene Crevel, Ph.D.
Steven M. Gendel, Ph.D.
Susan Hefle, Ph.D.
Stefano Luccioli, M.D.
Anne Munoz-Furlong
Steve Taylor, Ph.D.
Robert Wood, M.D.

GUEST SPEAKERS (July 14, 2005):

Catherine Copp, J.D.
Pekka Collin, M.D., M.P.H.
Alessio Fasano, M.D.
Steven M. Gendel, Ph.D
Rhonda R. Kane, M.S., R.D.
Donald Kasarda, Ph.D.
Cynthia Kupper, R.D., C.D.
Joseph A. Murray, M.D.

FDA Charge to the Committee

The Food Advisory Committee is being asked to evaluate the CFSAN Threshold Working Group Draft Report "Approaches to Establish Thresholds for Major Food Allergens and For Gluten in Food." The Committee should advise the FDA whether the draft report is scientifically sound in its analyses and approaches and whether the draft report adequately considers available relevant data on major food allergens and on gluten. In addressing these issues, FDA requested that the Committee consider specific questions (see below).

The Committee Responses to FDA's General Questions about Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food

- 1. In addition to the four approaches identified by FDA for establishing thresholds (i.e., analytical methods-based, safety assessment-based, risk assessment-based and statutorily-derived) are there other approaches that FDA should consider? If so, please describe and explain why FDA should consider them.*

The Committee concluded that CFSAN's Draft Report includes a complete evaluation of the currently available data and descriptions of all relevant approaches that could be used to establish thresholds for major allergens and gluten in food. No additional approaches were identified. The differences between the safety assessment-based and risk assessment-based approaches were discussed. The Committee suggested that, while these approaches are distinct, they are not mutually exclusive. For example, the Committee stated that statistical analyses could be incorporated into a traditional safety assessment-based approach by considering dose-response distributions. It was also suggested that safety assessments could make use of population-based data in addition to clinical challenge studies to estimate NOAELs and LOAELs. The Committee agreed with FDA that the risk assessment-based approach is scientifically the strongest of the approaches, and that this approach should be used in a transparent manner with appropriate consideration of data uncertainties, when sufficient data become available. One Committee member, however, also stated that the risk assessment-based approach could be used with limited data if the associated uncertainties are considered in a transparent manner. One Committee member suggested that an effort should be made to extend the analytical methods-based approach beyond the testing of foods to the measurement of biomarkers, such as the T-cell

amplification of response in Celiac disease patients.

- 2. Are FDA's criteria for selecting and evaluating the available data appropriate? If not, should any of the criteria be modified or deleted? Please describe any changes you would like to see and why. Are there additional criteria FDA should consider?*

The Committee agreed that the criteria identified in the Report for selecting and evaluating available data were appropriate. One Committee member noted that a technology assessment prepared for the Agency for Healthcare Research and Quality identified a similar set of criteria for evaluating published clinical data and suggested that the FDA use that technology assessment as an additional resource. Another committee member stated that it is important that adequate descriptions of the specific analytical methods be available so that potential biases or weaknesses inherent within them can be examined. It was also mentioned that the number of patients in each study should be included in the summary table of published oral challenge studies (Appendix 2).

- 3. Recognizing that some of the key studies (i.e., challenge studies) are ongoing, what if any use of preliminary data that have not been peer-reviewed for establishing thresholds is appropriate?*

The Committee recommended that data from highly-relevant, well designed studies be considered, even if they have not yet been published or peer-reviewed. One Committee member stated that unpublished or informal information can be collected and used and that there are accepted procedures for obtaining and documenting opinions provided by experts. These procedures could also be used to collect data such as those from clinicians that have individual patient data on NOAELs and LOAELs, while recognizing the limitations of that data. It was noted that ancillary data, while not suitable for direct use in safety or risk assessments, may be helpful in specifying uncertainty factors. The Committee also recommended that FDA contact the European Food Safety Authority, the European Commission, and Health Canada to determine if they have additional data.

The Committee's Responses to FDA's Specific Questions on Food Allergens

- 1. Are there distinct subpopulations of highly sensitive individuals within the allergic population for each of the major food allergens? If so, for the safety-assessment-based approach, are the proposed uncertainty factors for intraspecies differences (10-fold) and severity of responses for this sensitive population (10-fold) sufficient to ensure that exposure levels will be below the level of sensitivity for the highly sensitive populations? If these uncertainty factors (total of 100-fold) are not sufficient, what uncertainty factors should be used for the safety-assessment-based approach?*

The Committee felt that it is not possible at this time to identify distinct subpopulations within the allergic population by clinical criteria, previous frequency or severity of allergic reactions, or responses in a double-blind, placebo-controlled, food challenges.

The Committee stated that, unlike classical toxicological safety assessments, the uncertainty factor for highly sensitive food allergic populations is unknown. The selection of this uncertainty factor should be based on the distribution of the NOAELs and LOAELs using measures of data spread such as standard deviation and interquartile ranges. If reproducible, subjective responses in patients with a history of life-threatening anaphylaxis are used to determine LOAELs and NOAELs, an uncertainty factor less than 10 may be appropriate because the number of extremely sensitive individuals included in studies is likely to increase in this type of design.

Additionally, the Committee discussed the fact that caution is needed in using currently available data to determine LOAELs and NOAELs for allergens due to the exclusion of sensitive individuals who have experienced life-threatening allergic reactions (anaphylaxis) from clinical studies. All currently available published and unpublished data should be specifically assessed for potential selection or referral bias, and for other factors that influence the choice of individuals who are actually studied. There are also uncertainties associated with variation between individuals within a population and variation within individuals over time. Existing prospective studies performed with the goal of determining whether objective response thresholds in patients with persistent food allergy change over time are inadequate, except for those that measure the development of tolerance.

A highly sensitive individual might have a lower or higher LOAEL compared to baseline depending on such factors as: the season of year (changes in histamine release potential related to seasonal allergic diseases), status of atopic dermatitis; the time of day; stability of the patient's underlying asthma, ingestion of other substances such as alcohol, exercise, food matrix effects, food processing effects, and progression the disease based factors such as IgE target epitope diversification, antibody increases, and other variables which are known to those working in this field.

The Committee did not suggest a specific uncertainty factor. They noted that uncertainty factors of 10-fold or a 100-fold had been used in biomedical toxicology. IgE-mediated allergic reactions amplify reactions to minute amounts of allergens. Therefore, several Committee members felt that the application of uncertainty factors to thresholds based on the double-blind, placebo-controlled, food challenges may not be sufficiently large to handle this variation of amplification of an allergic response. It was further noted that uncertainty factors should account for the range of sensitive individuals.

Additional advice offered by the Committee included the following:

- 1) The risk assessment-based approach, using modeling techniques, does not require the use of uncertainty factors and is a promising approach when adequate data are available.
- 2) When establishing thresholds, one Committee member stated that it is important to consider whether an analytical method exists that is capable of verifying whether foods comply with these threshold levels. However, another Committee member stated that lack of adequate analytical sensitivity should not temper the science or affect the determination of uncertainty factors, but that this consideration should be made transparent.

3) One Committee member also mentioned that, from a statistical perspective, the first step in actually setting a threshold should be to define the precise goal of the threshold in terms of the sensitive population, and the acceptable risk level.

4) The Committee noted that it is not always clear in the published literature whether a particular study was a population-based, randomized-control trial representative of the population of allergic individuals or whether there was bias in the selection of test subjects because of exclusion criteria and or because the participants were all referred to the trial.

5) The Committee also discussed the practical implications of various manufacturers' labeling products in relation to the needs of consumers to have the information needed to make product choices.

2. Is the initial objective response seen in a clinical challenge study always an adverse effect that poses risk to human health? Is it scientifically sound to use this response to determine a LOAEL in the absence of a NOAEL? For the safety-assessment-based approach, is the proposed uncertainty factor of 10-fold sufficient and appropriate to use in the absence of a NOAEL? If a clinical challenge study reports a subjective response of a lower dose than the dose that caused an objective response, should that observation be taken into account when determining the appropriate uncertainty factor?

The Committee agreed that if there is an objective response to a food in a double-blind, placebo-controlled study performed in a patient with IgE-mediated food allergy, this is an adverse effect that poses risk, albeit usually low. The finding of an objective response in a double-blind, placebo-controlled, food challenge is sufficient for a physician to make recommendations that patients avoid specific foods and change lifestyle to avoid risk of life-threatening allergic responses. Therefore, it is appropriate to conclude that objective responses associated with allergic reactions pose risks to human health. The Committee also indicated that data on subjective reactions can be very useful in establishing appropriate uncertainty factor(s). For example, it was noted by one Committee member that in one specific food challenge study, there was a 20-fold difference in one patient and a 50-fold difference in another between the dose required for a subjective response and the initial objective response.

The Committee indicated that when a reaction occurs to the first administered dose in a clinical trial, it is not possible to know how much lower the LOAEL might be for that patient. In that case, it would not be scientifically sound to use that response to determine a LOAEL in the absence of a NOAEL. Similarly, in this situation the proposed uncertainty factor of 10-fold would not be sufficient nor appropriate to use in the safety-assessment-based approach.

The Committee also stated that LOAELs should be based on objective responses. However, when a challenge study recorded the dose at which both subjective and objective responses occurred, that information can be used to select the appropriate uncertainty factor(s). A smaller uncertainty factor might be needed if the doses that result in the initial objective response and the subjective response are similar.

While objective responses are preferred, the Committee acknowledged that there is controversy as to the applicability of LOAELs based on subjective responses. The Committee concluded that it would be scientifically useful if both subjective and objective reactions are recorded in oral challenge studies in order to learn more about the relationship between the two. It was further mentioned that standards for performing challenge studies are needed that should include assessment of the potential study biases or sources of error (such as referral bias, selection bias, disease-spectrum bias, verification bias) and potential confounding factors (such as time of day, season, exercise, concurrent medications). In addition, the Committee noted that recruitment of highly sensitive subpopulations for challenge studies may be enhanced by recording reproducible subjective reactions (two challenges each with the active dose and placebo), with an option of stopping at that dose. Highly sensitive patients may or may not be willing to proceed to an objective response or the physician may not be comfortable proceeding.

3. In the absence of specific data that would allow thresholds to be established for each of the major food allergens, is it scientifically sound to use the threshold established for a single food allergen (e.g., peanuts) as the threshold for all major food allergens? If so, which food or foods could serve this function? If not, is there a more appropriate method to use?

Opinions differed among the members of the Committee as to whether it is scientifically sound to use the threshold established for a single food allergen as the threshold for other allergens. Some members agreed that given the lack of data for all allergens, it is reasonable to establish thresholds for some allergens based on the thresholds for other, potent allergens until more data are available for specific allergens. However, there was no consensus as to whether this was appropriate in all cases or whether peanut was an appropriate comparator since, for example, a threshold for soy might be higher than for peanut. 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. It was also noted that the acceptable level of uncertainty can be different for a parent making a decision about food exposure for a child, a physician making diet recommendations for a patient, and an agency making policy recommendations for consumers and industry.

4. The draft report discusses the available data on the levels of protein present in highly refined oils (e.g., oil that is hot solvent extracted, refined, bleached, and deodorized). Is there any physiologic reason (e.g., food matrix effect, denaturation of protein) why the protein levels in highly refined oils could not be used as the basis for establishing a threshold for other allergenic foods? Are there any other limitations that should be considered in applying this approach to the eight allergenic foods?

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 structures 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.

The Committee's Responses to FDA's Specific Question on Gluten in Food

1. Is there a distinct subpopulation of individuals with celiac disease that have an increased sensitivity to gluten? If so, for the safety-assessment-based approach, is the proposed uncertainty factor for intraspecies differences (10-fold) sufficient to ensure that exposure levels will be below the level of sensitivity for this highly sensitive subpopulation? If this uncertainty factor (10-fold) is not sufficient, what uncertainty factors should be used?

Sensitivity to gluten varies from one individual to another at the level of clinical symptoms. However, symptoms of celiac disease do not parallel small intestinal mucosal injury as assessed by small bowel biopsy histology, which is the widely accepted quantitative method for assessing gluten-induced injury in celiac disease. There are insufficient available data to state with any certainty whether, or to what extent, individual variations influence the intestinal mucosal changes in response to specific levels of gluten exposure. Thus, it is not possible currently to assign a reliable uncertainty factor for intraspecies differences in gluten sensitivity.

The Committee was uncertain as to whether or not it is appropriate to apply an uncertainty factor based on the standards normally used for toxicology studies for intraspecies variation to the immunological responses to gluten that occur in celiac disease. The magnitude of the uncertainty factor would be influenced by the level of individual variation observed in the studies used to determine that threshold. The choice of an uncertainty factor for a dietary gluten threshold will also be influenced by the ability to measure the gluten content of foods. It is likely that the gluten threshold together with a modest or moderate uncertainty factor will lie close to the lower limits of performance of the currently available assays and this may, at least in the short-term, dictate the measurable threshold.

2. Is it scientifically sound to use data from short-term clinical studies that evaluate the effects of acute gluten exposure to predict the effects of long-term gluten exposure in gluten-sensitive individuals? What uncertainty factor is appropriate for thresholds developed using available short-term clinical studies in order to prevent adverse effects associated with chronic effects?

Data from acute challenge studies that examine intestinal mucosal changes in response to brief exposure to gluten peptides of several hours or days' duration are not widely accepted as valid for determining a gluten threshold. However, the Committee felt that there is general agreement in the medical and scientific community that data from studies that examine mucosal responses to exposures over several weeks or months are valid, and that the uncertainty factors needed to account for chronic exposure are minimal. One Committee member also stated that from a statistical perspective, uncertainty must be considered when using a 3-month exposure study to represent cumulative, chronic exposure, even though the observational data suggest that the responses seen after 3 months of exposure are similar to those from longer term exposure. Another Committee member commented on the importance of clearly documenting the evidence

used to determine the uncertainty factor, so that experts and others can properly review and comment on the factor and the data used to develop it.

The Committee felt that additional valuable data may also be available from other countries, particularly in Europe, that have many years of experience with the effects of threshold values. Those data may also reduce concerns regarding the need for an increased uncertainty factor based on prolonged duration of gluten exposure. Since a determination of threshold values must be made in the context of incomplete and evolving medical and scientific knowledge, the Committee endorses the Working Group's finding that any threshold value that may be set for gluten must be continually reevaluated, and, if new information warrants, be adjusted.

3. Are current data sufficient to conclude that a portion of celiac patients are (or are not) also susceptible to gluten proteins naturally occurring in oats (i.e., prolamines and glutelin)? If not, what additional data is needed to draw such a conclusion?

Published data indicate that the majority of individuals with celiac disease do not demonstrate significant symptoms or signs in response to the ingestion of oats. A meta-analysis of these published studies may serve to strengthen this conclusion. There are a very small number of documented cases where individuals with celiac disease showed an immune-based response to oat proteins. However, the low frequency of these reports indicates that the overall approach to setting a threshold for gluten should not be unduly influenced by the relatively minor concern of oat-sensitivity. Of greater concern is the issue of cross-contact leading to low-level contamination of foodstuffs with the known gluten proteins.

4. Are all individuals with celiac disease equally at risk for developing consequences (e.g., cancer) and increased mortality from the long-term ingestion of gluten? Are current data from clinical studies or from individuals with celiac disease on a gluten-restricted diet sufficient to estimate the magnitude of any increased risk of mortality for these individuals?

The long term consequences of celiac disease vary widely between individuals, from lifelong silent disease to fatal malignancy. However, at this time, the only identified risk factor for experiencing severe consequences, including death from malignancy, is poor or no compliance with a gluten-free diet. Prolonged, strict adherence to a gluten-free diet clearly reduces the risk for gastrointestinal symptoms and nutritional deficiencies such as anemia and osteoporosis. The available data, though limited and imperfect, indicate that prolonged, strict adherence to a gluten-free diet also reduces the risk for malignancy. Thus, instituting measures that facilitate compliance with a strict gluten-free diet are the only known approaches to reducing the overall risks associated with celiac disease.

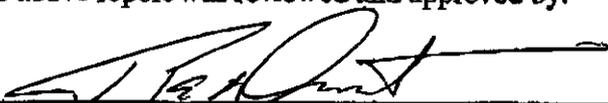
5. Is evidence of minimal intestinal pathological change (e.g., increased intraepithelial lymphocytes) following a gluten challenge, an appropriate symptom upon which to base a

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5. Is evidence of minimal intestinal pathological change (e.g., increased intraepithelial lymphocytes) following a gluten challenge, an appropriate symptom upon which to base a LOAEL for long-term consequences? Are other biomarkers such as clinical symptoms or more severe intestinal pathological changes, more accurate predictors of long-term consequences?

The Committee stated that characteristic intestinal pathological changes such as reduced villus-to-crypt ratio and increased intraepithelial lymphocyte counts constitute an appropriate widely accepted gold standard for diagnosis of celiac disease. These changes are also widely accepted as the gold standard for evaluating disease activity following a gluten challenge. Other disease markers such as anti gliadin antibody, tissue transglutaminase or endomysial antibody levels, or measures of mucosal permeability are considered to be of secondary value.

The above report was reviewed and approved by:



Dr. Richard Durst, Chairman of the referenced meeting held July 13-15, 2005



Marcia L. Moore, Executive Secretary of the Food Advisory Committee