



THAI AGRICULTURAL STANDARD

TAS 9011-2006

**ASSESSMENT OF POSSIBLE
ALLERGENICITY**

**National Bureau of Agricultural Commodity and Food Standards
Ministry of Agriculture and Cooperatives**

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National Bureau of Agricultural Commodity and Food Standards

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Since newly expressed proteins that may present in foods derived from Recombinant-DNA technology may induce allergic reactions and cause allergic sensitization in some individuals, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, had developed the guideline for assessment of possible allergenicity to be used as a guideline in several countries. However, at present, there is no definitive test that can be relied upon to predict allergic response in humans to a newly expressed protein; therefore, an approach taking into account the evidence derived from several types of information and data is used in the assessment of possible allergen of newly expressed proteins.

According to the international acceptance of the Codex Guideline for Assessment of Possible Allergenicity, it is appropriate to establish a national standard which is based on the Codex guideline.

The establishment of this standard is based on the following documents:

FAO/WHO. 2004. Annex to Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants: Assessment of Possible Allergenicity, pp. 22-26. In Codex Alimentarius Commission: Foods Derived from Biotechnology. Joint FAO/WHO Food Standards Programme, FAO, Rome.

FAO/WHO. 2004. Annex to Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms: Assessment of Possible Allergenicity, pp. 47-51. In Codex Alimentarius Commission: Foods Derived from Biotechnology. Joint FAO/WHO Food Standards Programme, FAO, Rome.

Remark:

The standard title has been revised from “Thai Agricultural Commodity and Food Standard (TACFS)” to “Thai Agricultural Standard (TAS)” in accordance with the enforcement of the Agricultural Standards Act B.E. 2551 (2008).



**NOTIFICATION OF THE NATIONAL COMMITTEE ON
AGRICULTURAL COMMODITY AND FOOD STANDARDS
SUBJECT: THAI AGRICULTURAL COMMODITY AND FOOD STANDARD:
ASSESSMENT OF POSSIBLE ALLERGENICITY
B.E.2549 (2006)**

The resolution of the 1/2549 session of the National Committee on Agricultural Commodity and Food Standards dated 8 June B.E. 2549 (2006) endorsed the Thai Agricultural Commodity and Food Standard entitled Assessment of Possible Allergenicity. This standard would be of benefits for quality improvement, facilitating trade and protecting consumers.

By virtue of the Cabinet Resolution on Appointment and Authorization of the National Committee on Agricultural Commodity and Food Standards dated 19 November B.E.2545 (2002), the Notification on Thai Agricultural Commodity and Food Standard entitled Assessment of Possible Allergenicity is hereby issued as voluntary standard, the details of which are attached herewith.

Notified on 19 July B.E.2549 (2006)

Khunying Sudarat Keyuraphan

Minister of Agriculture and Cooperatives

Chairperson of the National Committee on Agricultural Commodity and Food Standards

THAI AGRICULTURAL STANDARD

ASSESSMENT OF POSSIBLE ALLERGENICITY

1 INTRODUCTION

All newly expressed proteins^{1/} produced by recombinant-DNA organisms that could be present in the final food should be assessed for their potential to cause allergic reactions. This should include consideration of whether a newly expressed protein is one to which certain individuals may already be sensitive as well as whether a protein new to the food supply is likely to induce allergic reactions in some individuals.

At present, there is no definitive test that can be relied upon to predict allergic response in humans to a newly expressed protein, therefore, it is recommended that an integrated, stepwise, case by case approach, as described below, be used in the assessment of possible allergenicity of newly expressed proteins. This approach takes into account the evidence derived from several types of information and data since no single criterion is sufficiently predictive.

The endpoint of the assessment is a conclusion as to the likelihood of the protein being a food allergen.

2 ASSESSMENT STRATEGY

The initial steps in assessing possible allergenicity of any newly expressed proteins are the determination of:

- (1) the source of the introduced protein;
- (2) any significant similarity between the amino acid sequence of the protein and that of known allergens; and
- (3) its structural properties, including but not limited to, its susceptibility to enzymatic degradation, heat stability and/or, acid and enzymatic treatment.

As there is no single test that can predict the likely human IgE response to oral exposure, the first step to characterize newly expressed proteins should be the comparison of the amino acid sequence and certain physicochemical characteristics of the newly expressed protein with those of established allergens in a weight of evidence approach. This will require the isolation of any newly expressed proteins produced by recombinant-DNA organisms, or the synthesis or production of the substance from an alternative source, in which case the material should be shown to be structurally, functionally and biochemically equivalent to that produced by recombinant-DNA organisms. Particular attention should be given to the choice of the expression host, since post-translational modifications allowed by different hosts (i.e.:

^{1/} This assessment strategy is not applicable for assessing whether newly expressed proteins are capable of inducing gluten-sensitive or other enteropathies. The issue of enteropathies is already addressed in the Section on Assessment of Immunological Effects in Thai Agricultural Standard on Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (TAS 9012). In addition, the strategy is not applicable to the evaluation of foods where gene products are down regulated for hypoallergenic purposes.

eukaryotic vs. prokaryotic systems) may have an impact on the allergenic potential of the protein.

It is important to establish whether the source is known to cause allergic reactions. Genes derived from known allergenic sources should be assumed to encode an allergen unless scientific evidence demonstrates otherwise.

3 INITIAL ASSESSMENT

3.1 SOURCE OF THE PROTEIN

As part of the data supporting the safety of foods produced using recombinant-DNA organisms, information should describe any reports of allergenicity associated with the donor organism. Allergenic sources of genes would be defined as those organisms for which reasonable evidence of IgE mediated oral, respiratory or contact allergy is available.

Knowledge of the source of the introduced protein allows the identification of tools and relevant data to be considered in the allergenicity assessment. These include: the availability of sera for screening purposes; documented type, severity and frequency of allergic reactions; structural characteristics and amino acid sequence; physicochemical and immunological properties (when available) of known allergenic proteins from that source.

3.2 AMINO ACID SEQUENCE HOMOLOGY

The purpose of a sequence homology comparison is to assess the extent to which a newly expressed protein is similar in structure to a known allergen. This information may suggest whether that protein has an allergenic potential. Sequence homology searches comparing the structure of all newly expressed proteins with all known allergens should be done. Searches should be conducted using various algorithms such as FASTA or BLASTP to predict overall structural similarities. Strategies such as stepwise contiguous identical amino acid segment searches may also be performed for identifying sequences that may represent linear epitopes. The size of the contiguous amino acid search should be based on a scientifically justified rationale in order to minimize the potential for false negative or false positive results^{2/}.

IgE cross-reactivity between the newly expressed protein and a known allergen should be considered a possibility when there is more than 35% identity in a segment of 80 or more amino acids or other scientifically justified criteria. All the information resulting from the sequence homology comparison between the newly expressed protein and known allergens should be reported to allow a case-by-case scientifically based evaluation.

Sequence homology searches have certain limitations. In particular, comparisons are limited to the sequences of known allergens in publicly available databases and the scientific literature. There are also limitations in the ability of such comparisons to detect non-contiguous epitopes capable of binding themselves specifically with IgE antibodies.

^{2/} It is recognized that the 2001 FAO/WHO consultation suggested moving from 8 to 6 identical amino acid segment searches. The smaller the peptide sequence used in the stepwise comparison, the greater the likelihood of identifying false positives, inversely, the larger the peptide sequence used, the greater the likelihood of false negatives, thereby reducing the utility of the comparison.

A negative sequence homology result indicates that a newly expressed protein is not a known allergen and is unlikely to be cross-reactive to known allergens. A result indicating absence of significant sequence homology should be considered along with the other data outlined under this strategy in assessing the allergenic potential of newly expressed proteins. Further studies should be conducted as appropriate (see also sections 4 and 5). A positive sequence homology result indicates that the newly expressed protein is likely to be allergenic. If the product is to be considered further, it should be assessed using serum from individuals sensitized to the identified allergenic source.

3.3 PEPSIN RESISTANCE

Resistance to pepsin digestion has been observed in several food allergens; thus a correlation exists between resistance to digestion by pepsin and allergenic potential^{3/}. Therefore, the resistance of a protein to degradation in the presence of pepsin under appropriate conditions indicates that further analysis should be conducted to determine the likelihood of the newly expressed protein being allergenic.

The establishment of a consistent and well-validated pepsin degradation protocol may enhance the utility of this method. However, it should be taken into account that a lack of resistance to pepsin does not exclude that the newly expressed protein can be a relevant allergen.

Although the pepsin resistance protocol is strongly recommended, it is recognized that other enzyme susceptibility protocols exist. Alternative protocols may be used where adequate justification is provided.^{4/}

4 SPECIFIC SERUM SCREENING

For those proteins that originate from a source known to be allergenic, or have sequence homology with a known allergen, testing in immunological assays should be performed where sera are available. Sera from individuals with a clinically validated allergy to the source of the protein can be used to test the specific binding to IgE class antibodies of the protein in *in vitro* assays. A critical issue for testing will be the availability of human sera from sufficient numbers of individuals^{5/}. In addition, the quality of the sera and the assay procedure need to be standardized to produce a valid test result. For proteins from sources not known to be allergenic, and which do not exhibit sequence homology to a known allergen, targeted serum screening may be considered where such tests are available including targeted serum screening (i.e. the assessment of binding to IgE in sera of individuals with clinically validated allergic responses to broadly-related categories of foods) as described in Section 5.

^{3/} The method outlined in the U.S. Pharmacopoeia (1995) was used in the establishment of the correlation (Astwood *et al.*, 1996).

^{4/} Reference to Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology (2001) : Section "6.4 Pepsin Resistance.

^{5/} According to the Report of the Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology (22-25 January 2001, Rome, Italy) a minimum of 8 relevant sera is required to achieve a 99% certainty that the new protein is not an allergen in the case of a major allergen. Similarly, a minimum of 24 relevant sera is required to achieve the same level of certainty in the case of a minor allergen. It is recognized that these quantities of sera may not be available for testing purposes

In the case of a newly expressed protein derived from a known allergenic source, a negative result in *in vitro* immunoassays may not be considered sufficient, but should prompt additional testing, such as the possible use of skin test and *ex vivo* protocols^{6/}. A positive result in such tests would indicate to a potential allergen.

5 OTHER CONSIDERATIONS

The absolute exposure to the newly expressed protein and the effects of relevant food processing will contribute toward an overall conclusion about the potential for human health risk. In this regard, the nature of the food product intended for consumption should be taken into consideration in determining the types of processing which would be applied and its effects on the presence of the protein in the final food product.

As scientific knowledge and technology evolves, other methods and tools may be considered in assessing the allergenicity potential of newly expressed proteins as part of the assessment strategy. These methods should be scientifically sound and may include targeted serum screening (i.e. the assessment of binding to IgE in sera of individuals with clinically validated allergic responses to broadly-related categories of foods); the development of international serum banks; use of animal models; and examination of newly expressed proteins for T-cell epitopes and structural motifs associated with allergens.

^{6/} *Ex vivo* procedure is described as the testing for allergenicity using cells or tissue culture from allergic human subjects (Report of Joint FAO/WHO Expert Consultation on Allergenicity of Foods derived from Biotechnology).