

The Canadian Criteria for the Establishment of New Priority Food Allergens: Evidence for the Inclusion of Mustard and Insufficient Evidences for Garlic and Onion as Priority Allergens in Canada

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May 5, 2010





Objectives

- Allergen Labelling Regulation Background
- Development of HC Criteria's To Add Allergens to the Canadian Priority Allergens List
- Mustard as Potential Food Allergen Systematic Review
- Results and Conclusions
- Onion and Garlic as Potential Food Allergen Systematic Review
- Results and Conclusions
- Questions?





Canada Food and Drug Regulations

- ❑ Require that a complete and accurate list of ingredients appear on the label of most pre-packaged foods
- ❑ However, there are exemptions in the regulations e. g. when flavours, flour, seasoning and margarine are used as ingredients in other foods, their components do not have to be included in the list of ingredients
- ❑ Ingredient name may be confusing e.g.: *ovalbumin for egg, casein for milk.*
- ❑ *As a result, food allergens, gluten sources and added sulphites can be “hidden” from consumers trying to identify them in the list of ingredients.*
- ❑ Food allergens, if not declared in the list of ingredients, can pose a risk to allergic consumers. To alleviate this risk, only the food allergens need to be declared, not all components of the ingredient





HC proposed amendments to the *Food and Drug Regulations*

<http://www.hc-sc.gc.ca/fn-an/label-etiquet/allergen/index-eng.php>

- ❑ To enhance food labelling as a *public health tool* for food allergic consumers, enabling consumers to avoid allergens to which they are susceptible and allowing informed choices of safe food sources.
- ❑ The proposed regulatory amendments would require the declaration of potential hidden sources of priority food allergens in pre-packaged food products.





Proposed Regulatory Amendment

- ❑ The definition of a food allergen emphasizes the protein portion of the food responsible for eliciting an allergic reaction
- ❑ The protein from any of the defined food allergens, or any modified protein or any protein fraction that is derived from any of these foods, is considered a health risk to individuals with food allergies
- ❑ Consider other relevant factors in the Canadian context, particularly in terms of risk management for example allergen cross-reactivity





Proposed Regulatory Amendment

- ❑ The source of **hydrolysed plant proteins**, starches and modified starches, and lecithins will need to be declared
- ❑ Food allergens and gluten sources will require **declaration by name e.g. malt (barley), either in the list of ingredients or at the end of the list of ingredients in a “contains statement”**.





Proposed Regulatory Amendment

- ❑ 1220 – Enhanced Labelling for Food Allergens and Gluten Sources and Added Sulphites

<http://www.hc-sc.gc.ca/fn-an/label-etiquet/allergen/index-eng.php>

- ❑ Published by Health Canada in July 2008 / Canada Gazette, Part I

- ❑ Followed by a period for public comment

- ❑ Approx. 140 comments were received

<http://www.hc-sc.gc.ca/fn-an/label-etiquet/allergen/sum-comm-exa-eng.php>





Need to Revise List of Priority Allergens

On its proposed allergen labelling regulations HC received comments from:

- the general public
- patient groups, health professionals
- consumer organizations, and governmental agencies
- some comments included the need to consider mustard, onion and garlic as potential food allergens of concern for Canadians





Why a Priority Food Allergen List?

- ❑ A relatively small number of foods are responsible for the majority of severe food allergic reactions
- ❑ A “priority” list of food allergens makes labelling more manageable for manufacturers and agencies responsible for enforcement activities
- ❑ Labelling regulations can require that those food allergens on the list are always indicated on the label (above and beyond any normal labelling requirements) allowing the allergic consumer to avoid those foods

Marion Zarkadas et al. Common Allergenic Foods and Their Labelling in Canada –A Review. Canadian Journal of Allergy and Clinical Immunology 4: 3, 1999





Adding New Priority Food Allergens

- ❑ Development of Canadian Criteria for the Establishment of New Priority Food Allergens

<http://www.hc-sc.gc.ca/fn-an/pubs/label-etiquet/crit/index-eng.php>

- ❑ Development of Methods for The Management And Evaluation of Scientific Information

- ❑ Scientific Evaluation of Mustard, Onion and Garlic as Potential Food Allergens





Canadian Criteria

For the Establishment of New Priority Food Allergens

HC adopted the criteria for amending the Codex list of priority allergens. In accordance with the JECFA guidelines including:

1. Credible cause-effect relationship, based on + DBPC food challenges or unequivocal reports of reactions with typical features of severe allergic or intolerance reactions
2. Reports of severe systemic reactions following exposure to the foodstuff
3. Assessment of available prevalence data in children and adults supported by appropriate clinical studies with subjects from the general population of several countries or alternatively available prevalence data from clinical studies with groups of allergy patients from several countries supported as per the first recommendation.





Additional Considerations

- ❑ The allergenic **potency** of a food or food ingredient
- ❑ The potential **exposure** of Canadians to the food or food ingredient; specific consideration as to whether the food or food ingredient may become **hidden in pre-packaged** food products for sale in Canada because it is exempt from declaration in the list of ingredients on food packages, as per subsections B.01.009 one and two of the *Canadian Food and Drug Regulations*
- ❑ Whether the food or food ingredient is subject to the Canadian proposed definition of a food allergen, which emphasizes that **the protein portion** of the food is responsible for eliciting an allergic reaction
- ❑ Consideration to other factors that may be applicable to the **Canadian scenario and relevant to risk management**. These factors may include, but are not limited to, consideration of allergen **cross-reactivity**





Methods for Assessment

The Canadian criteria will be applied to the assessment of scientific information obtained from a systematic review of available literature. Methods for the management and evaluation of available scientific information have been developed in order to ensure a consistent and transparent approach when assessing the potential allergenicity of a food or food ingredient (Pulido et al, 2010)

- ❑ Systematic Data Collection
- ❑ Criteria for Assessing the Strength-of-Evidence
- ❑ Organization and Tabulation of Data
- ❑ Criteria for Evaluating the Severity of Clinical Reactions





Systematic Data Collection

An electronic database search utilizing, but not limited to, current versions of the following databases: Ovid Medline, Ovid Embase, and FSTA Direct

❑ Include publication if -

- Relevant to humans (adults or children)
- Relevant to an allergy via oral exposure through foodstuff
- Relevant to the identification and characterization of the specific allergenic proteins

❑ Exclude publication if -

- Experimental study assessing the allergenicity using animal models or *in vitro* methods
- Relevant to humans but the route of exposure is not via the oral route through foodstuff e.g. occupational exposures (dermal/respiratory)





Assessing the Strength-of-Evidence

- ❑ Study designs follow guidelines established by the Joint Task Force on Practice Parameters comprised of specialists in the field of allergy and immunology (Chapman, J.A et al, 2006 Bernstein, 2008)

- ❑ The criteria used in descending order from the strongest to weakest, is as follows:
 - meta-analysis of randomized controlled trials
 - randomized controlled trials
 - non-randomized controlled trials
 - quasi-experimental studies
 - non-experimental descriptive studies (comparative, correlation, or case-controlled studies)
 - expert committee reports or opinions or clinical experience of respected authorities
 - laboratory-based studies





Organization and Tabulation of Data

Evidence from publications that fulfilled the strength-of-evidence parameters will be tabulated under the following categories:

1. Pivotal Clinical Studies (evidence from meta-analysis and randomized and non-randomized controlled trials)
2. Non-Pivotal Clinical Studies (evidence from quasi-experimental studies)
3. Other Relevant Studies (evidence from non-experimental descriptive studies (comparative/correlation))
4. Case reports (evidence from non-experimental descriptive studies)





Evaluation: Severity of Clinical Reactions

- ❑ **Severe** reactions include symptoms that are strongly associated with hypotension and hypoxia (life-threatening upper airway obstruction) or neurologic compromise: confusion, collapse, loss of consciousness, and incontinence
- ❑ **Moderate** reactions include diaphoresis, dizziness, pre-syncope, dyspnea, stridor, wheezing, chest/throat tightness, nausea, vomiting, and abdominal pain
- ❑ **Mild** reactions are limited to the skin (urticaria, erythema, and angioedema). However, when angioedema affects the face and involves the glottis, it is associated with hypoxia and graded as severe

Brown, S.G. (2004) Clinical features and severity grading of anaphylaxis. The Journal of allergy and clinical immunology, 114, 371-376





Characterization of Mustard



- ❑ Mustard is a herbaceous flowering plant (Angiospermae) belonging to the family Brassicaceae
- ❑ The major types of mustard seeds used in cooking and food processing are: white (*Sinapis alba* or yellow mustard), brown (*Brassica juncea* or oriental mustard) and black (*Brassica nigra* or black mustard)



- **All three types of mustard seed are available in North America. In fact, Canada is a world leader in the international mustard seed market accounting for about 35% of world production and 50% of global exports**

- ❑ The major allergen of mustard is a 2S albumin
 - seed storage protein composed of one heavy chain and one light chain (39 and 88 amino acids), linked by two disulfide bridges





Characterization of Mustard

- ❑ The major 2S albumin of yellow mustard is *Sin a 1*
 - a thermostable protein that is resistant to digestion by trypsin and degradation by other proteolytic enzymes
- ❑ The major allergen found in oriental mustard is *Bra j 1*
 - *Bra j 1* and *Sin a 1* have a homologous epitope implying that individuals sensitive to one species of mustard are likely to show sensitivity to other species
- ❑ Cross-sensitivity between other Brassicaceae species appears to be rare
 - It has been proposed that proteins in cruciferae leafy vegetables are more susceptible to digestion and thermal degradation than the allergenic proteins in mustard





Review of Mustard Data

- ❑ This assessment followed the method outlined earlier
- ❑ A total of 358 publications were identified through the database search
- ❑ Based on the inclusion and exclusion criteria, 42 publications were selected and considered relevant to the objectives of this review: 27 fulfilled the strength-of-evidence categorization and tabulation criteria, including
 - Two double-blind, placebo-controlled food challenge (DBPCFC) studies and one single-blind, placebo controlled food challenge (SBPCFC) study were identified in the literature

Health Canada Mustard Allergy

<http://www.hc-sc.gc.ca/fn-an/pubs/label-etiquet/mustard-moutarde/index-eng.php>

Pulido Olga M., Gillespie Z, and Godefroy SB, 2010





Review of Mustard Data

- ❑ Six non pivotal studies conducted using an open allergenicity assessment
- ❑ Three non-experimental descriptive studies
- ❑ 15 case reports of allergic responses to mustard were identified in the literature (2 were Canadian)
- ❑ 15 publications were not included in the risk analysis, but provided information with regard to the characterization of mustard and were considered relevant to the evaluation





Assessment Against Criteria for Inclusion

1. The existence of a **credible cause-effect relationship**, based upon positive double blind, placebo-controlled food challenges (DBPCFC) or unequivocal reports of reactions with typical features of severe allergic or intolerance reactions

Two DBPCFC studies and one single-blind, placebo controlled food challenge (SBPCFC) study were identified in the literature and assessed as supporting evidence for a credible cause-effect relationship





Assessment Against Criteria for Inclusion

2. Reports of severe systemic reactions following exposure to the foodstuff

Information from the case studies confirmed severe systemic reactions to mustard

- Anaphylactic reactions are reported in 2% of children and in up to 48% of adults with a confirmed mustard allergy
- In a Canadian case report, 2 out of 5 children described had severe reactions to the ingestion of mustard, which required emergency medical intervention





Assessment Against Criteria for Inclusion

3. Assessment of available prevalence data:

Prevalence data are not available for Canada or for many other regions of the world, however:

- ❑ mustard allergy could be estimated as the 3rd /4th most common food allergy among children in some regions of France
- ❑ mustard allergy is probably the most common allergy among spices
- ❑ mustard is affirmed on the most recent list of 14 allergens to be declared on labels (updated 2007) by the European Commission
- ❑ mustard is recognized as an allergen by the International Union of Immunological Societies (IUIS, 2009)





Assessment Against Criteria for Inclusion

- ❑ Consideration of the allergenic potency of the food or food ingredient
 - There is evidence within the database to support the conclusion that the amount of mustard required to elicit a reaction may be very small; however there is insufficient information to estimate a dose-threshold
 - One study found that 40 mg of mustard seasoning (equivalent to 13.5 mg mustard seeds and 0.8 mg of protein) provoked a reaction in one child.
 - One case report estimated the concentration of mustard in a dip responsible for causing a reaction as 0.15 mg of mustard in 100 mg of dip, other case reports only indicated that the amount of mustard associated with the allergic response was small or present in trace amounts





Assessment Against Criteria for Inclusion

- ❑ Consideration of the potential Canadian exposure to the food or food ingredient with specific consideration as to whether the food or food ingredient may become a hidden source of food allergens in pre-packaged food products for sale in Canada

There is potential for mustard to be hidden in a pre-packed food product and not appear on the ingredient list if it is part of a spice mixture, seasoning mixture or food flavour-enhancer preparation





Assessment Against Criteria for Inclusion

- ❑ Consideration of whether the food or food ingredient is subject to the Canadian proposed definition of a food allergen, which emphasizes that the protein portion of the food is responsible for eliciting an allergic reaction

Supporting evidence for mustard:

Sin a 1 is the seed storage protein in yellow mustard associated with allergic reactions. It is resistant to degradation by heat and digestive enzymes. The major allergen found in oriental mustard is ***Bra j 1***.

Bra j 1 and ***Sin a 1*** have a homologous epitope. These findings imply that individuals known to be sensitive to one species of mustard seed are likely to show sensitivity to other species





Assessment Against Criteria for Inclusion

- Additional consideration will also be given to other factors that are considered applicable to the Canadian scenario and relevant to risk management. For example, these factors may include, but are not limited to, consideration of allergen cross-reactivity.

Additional factors which make mustard allergy relevant to the Canadian scenario include:

- the potential cross reactivity between mustard and rape seed
- Canada is a major producer of both these crops
- sensitization to mustard can be acquired through dermal and respiratory exposure.





Conclusion of Assessment of Mustard

- Based on all the evidence presented it was concluded that mustard had met the Canadian criteria required to add new allergens to the list of priority allergens

Mustard will be added to the list of priority allergens in Canada. This change will take effect when the new allergen labelling regulations have been finalized and come into force



Characterization of Onions and Garlic

- ❑ Garlic and onion are herbaceous perennial flowering plants belonging to the family *Alliaceae*
- ❑ Garlic (*Allium sativum* L.), onions (*Allium cepa*), shallots (*Allium oschaninii*), leeks (*Allium porrum*) and chives (*Allium schoenoprasum*) are part of this family
- ❑ Volatile sulphur-containing compounds are responsible for their pungent flavour and odour as well as the health-promoting effects
- ❑ Garlic is one of the most investigated medicinal plants. During 1960 to 2007, more than 3000 papers were published on the chemistry and biological effects of garlic and garlic preparations





Review of Garlic and Onion Data

- ❑ This assessment followed the method outlined earlier
- ❑ A total of 411 publications were identified through the database search
- ❑ Based on the inclusion and exclusion criteria 36 publications were considered relevant to the assessment of garlic and/or onion as food allergens
 - 20 fulfilled the strength-of-evidence categorization and tabulation criteria as previously established to support regulatory recommendations
 - Other 16 publications provided information with regard to the characterization of garlic and onion





Review of Garlic and Onion Data

- ❑ Pivotal clinical studies: meta-analysis of randomized controlled trials, individual randomized controlled trials or non-randomized controlled trials **were not available** for the allergenicity assessment of either garlic or onion.
- ❑ 6 studies were identified in the literature that were conducted using an open allergenicity assessment that included garlic (2 studies), onion (1 study) or both garlic and onion (3 studies) as part of the foodstuffs tested
 - These studies did find some subjects with positive SPT, labial (LFC), serum specific IgE and RAST IgE





Review of Garlic and Onion Data

- ❑ Three non-experimental, descriptive studies were identified in the literature as being relevant to the assessment of the allergenicity of onion (1 study) and both garlic and onion (2 studies).
- ❑ A total of 12 case reports of allergic responses to garlic (6 cases), onions (5 cases) or both garlic and onion (1 case) were identified in the literature.
 - Reactions ranged from acute anaphylaxis to generalized skin manifestation.
 - The case reports provided evidence that the allergenic proteins in garlic and onions are susceptible to enzymatic digestion and/or heat





Assessment Against Criteria for Inclusion

1. The existence of a credible cause-effect relationship, based upon positive double blind, placebo-controlled food challenges (DBPCFC) or unequivocal reports of reactions with typical features of severe allergic or intolerance reactions.

In the absence of DBPCFC studies, supporting studies were evaluated as per the strength of evidence provided by the study designs

The available evidence is not sufficient to support the determination of a credible cause-effect relationship for the allergenicity of garlic and/or onion.





Assessment Against Criteria for Inclusion

2. Reports of severe systemic reactions following exposure to the foodstuff.

Anaphylactic reactions associated with the consumption of garlic and/or onions have been reported in specific cases, although the prevalence of severe anaphylaxis-type reactions reported to be associated with the ingestion of garlic and/or onion is considered low





Assessment Against Criteria for Inclusion

3. Assessment of available prevalence data in children and adults, supported by appropriate clinical studies with subjects from the general population of several countries or alternatively available prevalence data from clinical studies with groups of allergy patients from several countries supported as per the first recommendation

Currently, prevalence data are not available for Canada or other regions of the world.





Assessment Against Criteria for Inclusion

- ❑ Consideration of whether the food or food ingredient is subject to the Canadian proposed definition of a food allergen, which emphasizes that the protein portion of the food is responsible for eliciting an allergic reaction.

The **allergenic proteins** in garlic and onion that elicit systemic allergic reactions **have yet to be fully identified and characterized.**

- reports of tolerances to cooked garlic and/or onion indicate that the antigens are labile to heat and/or digestive processes.





Assessment Against Criteria for Inclusion

❑ Consideration of the allergenic potency of the food or food ingredient:

The lowest eliciting dose in the database was reported in a case who experienced laryngeal pruritus, rhinorrhea and coughing after ingesting 0.5g of garlic (30 mg protein)

❑ Consideration of the potential Canadian exposure to the food or food ingredient and for onion or garlic to be hidden in the ingredient list if part of one an exempted ingredient (spices)

- Evidence of heat instability of allergenic proteins, and amount required to elicit an allergic reaction mean that the potential risk of allergic reactions being elicited after the consumption of garlic and/or onion used as an undeclared spice or seasoning is considered minimal





Assessment Against Criteria for Inclusion

An assessment of the assembled evidence-base for garlic and/or onion does not fulfill the Canadian criteria required to add new allergens to the list of priority allergens

Although there is few scientific publication that suggests that some individuals may experience severe reactions to the consumption of garlic and/or onion, particularly if uncooked, the prevalence of food allergies to garlic and/or onion in children and adults remain unknown

There is insufficient evidence to establish a credible cause/effect relationship for oral allergenicity





Conclusion for Garlic and Onion

Based on the current database, the potential for severe allergic reactions as a result of hidden sources of garlic and/or onion in pre-packaged foods is considered minimal.

It is recommended at this time that garlic and/or onions not be included on the Canadian list of priority food allergens

<http://www.hc-sc.gc.ca/fn-an/pubs/label-etiquet/go-ao/index-eng.php>





Canada's New Priority List of Food Allergens

BUT NOT UNTIL THE REGULATORY AMENDMENTS ARE PASSED AND COME INTO FORCE

- Peanut
- Almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios and walnuts)
- Milk
- Eggs
- Fish, crustaceans (crab, crayfish, lobster, shrimp) and shellfish (e.g. clams, mussels, oysters, scallops)
- Sesame seeds
- Soy
- Wheat (including spelt and kamut, triticale)
- Sulphites (10 ppm and above)
- Mustard





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Acknowledgements

- ❑ Samuel Godefroy PhD, Director General, Food Directorate
- ❑ Zoe Gillespie, Toxicologist, Bureau of Chemical Safety (BCS)
- ❑ Sheila Dubois PhD, Senior Epidemiologist, Food Directorate
- ❑ Sébastien La Vieille MD, Visiting Scientist, France
- ❑ Michael Abbott, Food Allergens Program Manager, BCS





Thank You !

Questions?

