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Health Canada's Proposal to Amend the *Food and Drug Regulations* to Permit the Use of a Second Source (*Aspergillus niger* ASP72) of the Enzyme Asparaginase in Certain Food Products – December 2009.

Bureau of Chemical Safety
Food Directorate
Health Products and Food Branch

December 2009



Canada 

PURPOSE

This document provides information on Health Canada's proposal to amend the [Food and Drug Regulations](#) ("Regulations") to allow the enzyme asparaginase from the source organism *Aspergillus niger* ASP72 (*A. niger* ASP72) to be used in, or in the manufacture of, various standardised and unstandardised foods including bread, flour, whole wheat flour and other flours, French fries, potato chips and potato-based products, reaction flavours, and unstandardised cereal-based products such as cakes, biscuits, cookies and processed breakfast cereals. It includes a summary of the information considered by Health Canada scientists in their assessment of the safety of asparaginase.

BACKGROUND

Asparaginase is an enzyme that hydrolyses an amino acid, asparagine, to aspartic acid by hydrolyzing the amide in free asparagine. Asparagine is a precursor of acrylamide. Acrylamide can be formed in certain foods, when they are heated above 120°C, through a reaction between asparagine and reducing sugars, both of which are found naturally in certain foodstuffs. Hydrolysis of asparagine by asparaginase before the heating step effectively reduces acrylamide formation. Asparaginase can thus be used in asparagine and carbohydrate-containing foods that are heated above 120°C, such as bread and other baked cereal-based products, baked or fried potato-based products and reaction flavours to reduce the formation of acrylamide.

Dietary exposure to acrylamide has been identified as of potential concern by the [Joint FAO/WHO Expert Committee on Food Additives](#) (JECFA).¹

In Canada, enzymes used in food applications, such as asparaginase, may be considered food additives, depending on their conditions of use. Permitted food additives are listed in the food additive tables in Division 16 of the Regulations. Table V lists those food enzymes that may be used as food additives in Canada.

Before a new food additive is allowed to be used in Canada, a submission must be filed with Health Canada so that the Department can conduct a safety evaluation

¹ *Evaluation of certain food contaminants* (Sixty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series 930, 2006. Available at: <http://www.who.int/ipcs/publications/jecfa/reports/en/index.html>

of the proposed use(s) of the additive. Food manufacturers are not permitted to use the new additive until the safety assessment has been completed by Health Canada and the amendments to the Regulations that will enable the use of the additive are published in the *Canada Gazette* Part II.

CURRENT SITUATION

Health Canada has received two submissions for the use of asparaginase in foods. The first petition was for the use of asparaginase obtained from a genetically modified strain of *Aspergillus oryzae*. A [consultation document](#) concerning this source of asparaginase was posted on Health Canada's website in February 2009.

The second food additive submission sought the approval of the enzyme asparaginase from a different source organism, a genetically modified strain of *Aspergillus niger*. The food products covered by this second submission are various standardised and unstandardised foods including bread, flour, whole wheat flour and other flours, French fries, potato chips and potato-based products, reaction flavours, and unstandardised cereal-based products such as cakes, biscuits, cookies and processed breakfast cereals. Asparaginase, as used in the above foods, meets the regulatory definition of a food additive but is not currently listed in Table V, Division 16 of the Regulations.

Health Canada has completed a safety assessment of this second food additive submission for asparaginase and determined that there are no public health or safety concerns with the proposed use of this asparaginase. In addition, efficacy data have demonstrated that the use of asparaginase results in less acrylamide in foods. Therefore, Health Canada is proposing amendments to the Regulations to allow asparaginase to be used in the manufacture of bread, flour, whole wheat flour, and unstandardised foods.

SAFETY ASSESSMENT OF ASPARAGINASE

Health Canada scientists conducted a detailed and rigorous pre-market evaluation of the submission that focussed on safety. The evaluation considered the toxicological aspects of the proposed use of the additive, as well as relevant microbiological and molecular information, as described in this section.

Product Development and Formulation

A selected, pure culture of the production strain *Aspergillus niger* ASP72 (*A. niger* ASP72) was used to produce asparaginase through controlled submerged fermentation.

Under the Regulations, food enzyme preparations must meet the quality specifications of the *Food Chemicals Codex* (FCC). The enzyme preparation meets the general and additional requirements for enzymes as outlined in the FCC, and meets general specifications for enzyme preparations established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

Dietary Exposure

The potential intake of total organic solids (TOS) from the asparaginase preparation that was considered in the toxicological assessment was estimated to be 0.04 to 1.93 mg TOS/kg bw/day.

It is expected that the enzyme will be largely heat-inactivated during the manufacture and/or preparation of food (for example, during baking or frying).

Toxicological Assessment

Health Canada scientists had no toxicological objection to the proposed use of asparaginase from *A. niger* ASP72. The potential intake of the enzyme in comparison with the No Observable Effect Level (NOEL) of 1038 mg TOS/kg bw/day, derived from a 13-week oral toxicity study in rats, would have a margin of exposure of approximately 538-26,000 and is not a toxicological concern.

Microbial Assessment

A molecular and microbiological review of the production strain ASP72 and the enzyme manufacturing process was conducted by Health Canada scientists who noted that the genetic material potentially transferred to the microorganism is well-characterised, the production organism is not present in the final enzyme product, and the asparaginase preparation meets JECFA and FCC specifications for enzyme preparations. Based on this information, Health Canada scientists had no further questions from a molecular biology perspective.

RATIONALE FOR ACTION

- Dietary exposure to acrylamide has been identified as of potential concern by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Therefore, Health Canada is supportive, in general, of efforts by industry to find ways to reduce acrylamide in foods;
- The purpose for using asparaginase in food manufacturing is to reduce the risk of acrylamide formation in baked or fried food products. Enabling the use of asparaginase from a second source organism would provide the industry with another option for obtaining this enzyme for use in the production of foods sold in Canada;
- The information provided by the petitioner has satisfactorily met the requirements for a food additive submission as outlined in section B.16.002 of the Regulations.

INTERNATIONAL STATUS

Asparaginase from *A. niger* ASP72 is permitted for use in Australia, China, Denmark, Mexico, the Netherlands, New Zealand, Russia, Singapore, Switzerland and the United States, and has been assigned an acceptable daily intake (ADI) of “not specified” by JECFA.²

RECOMMENDATIONS

Through their evaluation of the submission, Health Canada scientists have concluded that the use of asparaginase from *A. niger* ASP72 as a food additive in bread, flour and whole wheat flour and unstandardised foods would not raise any health or safety concerns.

Given that asparaginase is a rather unique food additive that may be of benefit to the health of Canadians insofar as it can reduce acrylamide formation, Health Canada has assigned a high priority to enabling the use of asparaginase from acceptable source organisms. The Department has proposed amendments to the

² The JECFA evaluation is summarized in *Evaluation of certain food additives ; sixty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives* (WHO technical report series ; no.952), World Health Organization 2009. Accessible at: <http://www.who.int/ipcs/publications/jecfa/reports/en/index.html>

Regulations that will allow asparaginase from *A. niger* ASP72 to be used as a food additive in bread, flour and whole wheat flour, and unstandardised foods at a maximum level of use consistent with Good Manufacturing Practice (that is, the minimum amount needed for the intended technical effect).

The proposed listing for asparaginase from *A. niger* ASP72 would appear with a proposed listing for asparaginase from *Aspergillus oryzae* in Table V, Division 16 of the Regulations as follows:

<i>Column I Additive</i>	<i>Column II Permitted Source</i>	<i>Column III Permitted in or Upon</i>	<i>Column IV Maximum Level of Use</i>
Asparaginase	<i>Aspergillus niger</i> ASP72; <i>Aspergillus oryzae</i> (pCaHj621/BECh2#10)	(1) Bread (2) Flour and whole wheat flour (3) Unstandardised foods	(1) Good Manufacturing Practice (2) Good Manufacturing Practice (3) Good Manufacturing Practice

Bread, flour, and whole wheat flour have standards of identity in the Regulations that control which ingredients these foods may contain. Therefore, paragraph B.13.021(h) would be amended to allow asparaginase to be used in bread or white bread; paragraph B.13.001 (e)(iii) would be amended to allow asparaginase in flour, white flour, enriched flour or enriched white flour; and paragraph B.13.005 (d)(iii) would be amended to allow asparaginase in whole wheat flour or entire wheat flour.

The listing in Table V for asparaginase in unstandardised foods will enable use of asparaginase in foods such as cakes, cookies and biscuits, French fries, potato chips and other unstandardised potato-based products, reaction flavours and processed breakfast cereals. Although French fries do not have a standard of identity in the *Food and Drug Regulations*, frozen French fries are standardised under the *Processed Products Regulations* (PPR) which are administered by the Canadian Food Inspection Agency. Consequentially, amendments to the PPR will also need to be made to enable the use of asparaginase in frozen French fries.

COMMENTS

Comments on this proposal may be submitted in writing, either electronically or by regular mail. If you are submitting your comments electronically, please use the word "asparaginase" in the subject box of your e-mail. **Comments must be received by 12:00 a.m. EDT, on February 21, 2010. Please submit your comments to:**

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ADDITIONAL INFORMATION

For more information on this initiative, please contact the [Chemical Health Hazard Assessment Division](#).