Information Document on Health Canada's Proposal to amend the *Food and Drug Regulations* to allow the use of cross-linked carboxymethyl cellulose in table-top sweetener tablets

A PAHO/WHO Collaborating Center for Food Contamination Monitoring

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Bureau of Chemical Safety
Food Directorate
Health Products and Food Branch





Canada

Table of Contents

Purpose

This document provides information on Health Canada's proposal to amend the *Food and Drug Regulations* ("Regulations") to permit the use of cross-linked carboxymethyl cellulose in table-top sweetener tablets. Cross-linked carboxymethyl cellulose (cross-linked CMC) would be used as a disintegrant to decrease the time required for tablets to dissolve in beverages.

Background

In Canada, all food additives are regulated and subject to rigorous controls under the *Food and Drug Regulations* ("Regulations") and the *Food and Drugs Act.* Before a food additive is permitted for use, a submission must be filed with Health Canada's Food Directorate so the Department can conduct a safety evaluation of the proposed use(s) of the additive. Food manufacturers are not permitted to use a food additive until it has been approved by Health Canada and steps have been taken to legally enable their use, either through either an amendment of the Regulations or the issuance of an Interim Marketing Authorization.

Health Canada received a submission requesting that the Regulations be amended to permit the addition of L-leucine and cross-linked CMC at a level of 10% and 2% (w/w), respectively, in tablet formulations of sucralose-containing table-top sweeteners.

L-leucine is an amino acid permitted to be added to infant formulas and formulated liquid diets. A provision currently exists in Table VIII, Division 16, of the *Food and Drug Regulations* for the use of L-leucine, at 3% of tablet weight, as a lubricant in the manufacture of table-top sweetener tablets containing aspartame. As L-leucine is already an approved food additive under Division 16, the requested extension of use to a new food was eligible for an Interim Marketing Authorization (IMA) once the evaluation of the submission confirmed that there would be no human health concerns with the proposed use. As a result, the requested use of L-leucine as a lubricant and/or binder in table-top sweetener tablets at levels consistent with good manufacturing practice was enabled under an IMA that was published in the Government of Canada's official newspaper, the *Canada Gazette* (Part I, Vol. 142, No. 19) on May 10, 2008.

Cross-linked CMC is the product resulting from the treatment of carboxymethyl cellulose with acid and heat, and is not a permitted food additive in Canada. Although a related additive, carboxymethyl cellulose is currently permitted at different levels in a variety of foods as listed in Table IV, Division 16, of the Regulations, cross-linked CMC is considered a new food additive in Canada and istherefore not eligible for an IMA. As a result, cross-linked CMC is the focus of the current Information Document.

Current Situation

Health Canada's Food Directorate has completed a safety assessment of cross-linked CMC when used as described in the submission. As no safety concerns have been raised with the proposed use in sucralose-containing table-top sweetener tablets, the Department is proposing amendments to the Regulations to allow the proposed use of cross-linked CMC. Furthermore, based on the safety data, it is proposed that the use of this additive may be permitted in table-top sweeteners containing any of the sweeteners approved for such use in table-top sweeteners under Table IX, Division 16, of the Regulations. Such provisions would allow for the use of cross-linked CMC when there is a technological justification, that is, when the sweeteners are sold in tablet form. This approach is consistent with that taken for L-leucine, the use of which has previously been enabled in table-top sweetener tablets.

Safety Assessment

Health Canada's Food Directorate scientists have conducted a detailed and rigorous evaluation, focussed on safety and efficacy, of the submission for the use of cross-linked CMC in table-top sweetener tablets. Their evaluation considered chemical, toxicological and nutritional aspects of the proposed use of cross-linked CMC, as described in the following sections.

Chemical Assessment

The chemical safety information provided by the petitioner has been evaluated. The submission satisfactorily addressed all of the criteria appearing in Section B.16.002 of the Regulations and the petitioner demonstrated that the food additive meets the relevant specifications, which are those of the Joint WHO/FAO Expert Committee on Food Additives (JECFA).

Dietary Exposure

Dietary exposure to cross-linked CMC was estimated using the consumption of dry powder 100% sucralose-based sweetener containing 2% cross-linked CMC. Based on USDA consumption data, the Eaters Only, 90th percentile intake of cross-linked CMC was estimated to be 50 mg/day or 0.58 mg/ kg bw per day. The petitioner estimated 90th percentile intakes of cross-linked CMC from the sweetener tablets by a child, an adult male, and an adult female of 7.5 mg, 40 mg, and 50 mg respectively. On a body weight basis, these intakes correspond to 0.2 mg, 0.42 mg, and 0.61 mg/kg bw per day respectively.

Toxicological Assessment

Evaluation of the available data supports the use of cross-linked CMC in the manufacture of sucralose-containing tablet formulations at the proposed level of 2% (w/w).

A published study has demonstrated that carboxymethyl cellulose, the parent compound of cross-linked CMC, is poorly absorbed. Cross-linked CMC, being considered insoluble in water, would be absorbed even less than its parent compound, suggesting that cross-linked CMC would be even less likely to cause systemic toxicity than carboxymethyl cellulose.

JECFA has evaluated the toxicity of cross-linked CMC and established an acceptable daily intake (ADI) of "not specified". ADI's of "not specified" are only assigned to those food additives that are of very low toxicity and for which dietary exposure from its food additive uses (at levels consistent with good manufacturing practices) and any normal background levels does not present a hazard to health. JECFA's conclusion was based on the findings from high-quality 90-day feeding and teratology studies in rats, as well as the similarity of this chemical with carboxymethyl cellulose and other modified celluloses. JECFA has thoroughly studied the extensive toxicological database of this group of chemicals, three of which have been assigned ADIs of "not specified". JECFA also notes that, internationally, cross-linked CMC is used in table-top sweeteners and dietary food supplements to facilitate disintegration in aqueous solutions with a maximum level of use of 30 g/kg (3%).

The 90th percentile intakes of cross-linked CMC were observed to be between 0.2-0.61 mg/kg bw per day, which were several orders of magnitude lower than the No Observed Adverse Effect Level (NOAEL) of 3,992 mg/kg bw per day observed in a 90-day feeding study in male rats. The margin of exposure is considered sufficiently large that there would be no toxicity associated with the use of cross-linked CMC in the manner proposed by the petitioner.

Nutritional Assessment

There were no objections, based on nutritional considerations, to the use of cross-linked CMC at the proposed level of 2% tablet weight in the manufacturing of sucralose-containing table-top sweetener tablets. The conclusions of JECFA, as described in the Toxicological Assessment section above, were noted.

Other Considerations

Any person who intends to import or manufacture a new substance in Canada must submit a notification under the *New Substances Notification Regulations* (NSNR) prior to importing or manufacturing the substance. Under certain conditions, a new

substance will need to undergo an environmental assessment. Cross-linked CMC is not required to undergo an environmental assessment as a result of this proposal. Although cross-linked carboxymethyl cellulose (synonym, cross-linked sodium carboxymethyl cellulose, CAS 74811-65-7) is not on the Domestic Substances List (DSL), it is on the 1987-2001 In-Commerce List. According to the Environmental Assessment Unit of the Healthy Environments and Consumer Safety Branch, for uses of this compound that are regulated under the *Food and Drugs Act* uses only, notification under the NSNR would not be required at this time.

Rationale for Action

Given the acceptability of cross-linked CMC on toxicological, nutritional, chemical safety, and efficacy grounds, and the fact that the submission meets the requirements of section B.16.002 of the Regulations, it is proposed that the Regulations be amended to permit the use of cross-linked CMC in table-top sweeteners containing any of the sweeteners approved for such use under Table IX, Division 16, of the Regulations. As noted previously, this provision would allow for the use of this additive when there is a technological justification, that is, when the sweetener is sold in tablet form.

This proposal is expected to have no adverse impact on consumers, based on an assessment of safety.

International Status

Sucralose-containing table-top sweetener tablets are currently sold in the United States, United Kingdom and Australia/New Zealand. Cross-linked CMC is approved in the European Union (EU) as an additive under Directive 98/72/EC (European Parliament and Council, 1998) with the E number of E468 (Crosslinked sodium carboxy methyl cellulose). Cross-linked CMC (INS 468) was adopted in 2005 by the Codex Alimentarius Commission as an additive permitted for use in food in general, unless otherwise specified, in accordance with GMP (Table Three of the General Standard for Food Additives).

Previous Consultation

No external consultation was considered necessary during the safety evaluation since table-top sweeteners do not have a standard of identity in the Regulations. Furthermore, this proposal would not impose a new regulatory requirement on the food industry; rather, the proposal involves the introduction of enabling regulations. As noted previously, the requested use of L-leucine as a lubricant and/or binder in table-top sweetener tablets at levels consistent with good manufacturing practice was enabled under an IMA that was published in the Government of Canada's official newspaper, the *Canada Gazette* (Part I, Vol. 142, No. 19) on May 10, 2008. The publication of the IMA, which allowed for the use of L-leucine and announced

Health Canada's intention to amend the Regulations to reflect this permitted use, was followed by a 75 day period for the presentation of any public comments on the proposal.

Health Canada's Proposal

Health Canada's Health Products and Food Branch has a mandate and responsibility to review and approve food additives according to the requirements of section B.16.002 of the *Food and Drug Regulations*. This submission has been evaluated by Health Canada's Food Directorate pursuant to the requirements of section B.16.002 of the *Food and Drug Regulations*. It is considered that the submitted information satisfactorily meets the requirements of that section.

The petitioner had requested a maximum level of use of cross-linked CMC of 2% of tablet weight for sucralose-containing tablets. However, to be consistent with the general approach of permitting the use of food additives at levels consistent with GMP when the ADI is "not specified", it is proposed that cross-linked CMC be listed at levels consistent with GMP. Furthermore, the Food Directorate proposes that this food additive be permitted in "Table-top sweetener tablets containing sweeteners approved in Table IX for use in table-top sweeteners" instead of restricting its use to table-top sweetener tablets containing sucralose. Therefore, it is proposed that two new Items, C.12A and S.3C be created in Table VIII, Division 16 of the *Food and Drug Regulations* to read as follows:

Item No.	*Column I Additive*	*Column II Permitted in or Upon*	*Column III Purpose of Use*	*Column III Maximum Level of Use*
C.12A	Carboxy-methyl Cellulose, cross-linked	Table-top sweetener tablets containing sweeteners approved in Table IX for use in table-top sweeteners	Tablet disintegration	GMP

Item No.	*Column I Additive*	*Column II Permitted in or Upon*	*Column III Purpose of Use*	*Column III Maximum Level of Use*
S.3C	Sodium Carboxy-methyl Cellulose, cross-linked	Same foods as listed for Carboxymethyl Cellulose, cross-linked	Tablet disintegration	Same levels as prescribed for Carboxymethyl Cellulose, cross-linked

Cross referencing "cross-linked CMC" with its synonymous name "cross-linked sodium CMC" is consistent with the current listing for carboxymethyl cellulose.

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 words "**Cross-linked CMC**" in the subject box of your e-mail. **Comments must be received by 11:59 p.m. EST, October 11, 2011.**

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Additional Information

For more information on this initiative, please contact the Chemical Health Hazard Assessment Division at bcs-bipc@hc-sc.gc.ca. Please use the words "**Cross-linked CMC**" in the subject box of your e-mail.

This document is also available electronically, at:
www.healthcanada.gc.ca/foodadditives.