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**Information Document on Health Canada's Proposal
to Amend the *Food and Drug Regulations* to Permit
the use of Citric Acid Esters of Mono- and
Diglycerides (1) as a Food Additive in Infant
Formulae For Special Medical Purposes; and (2) in
those Foods that are Currently Permitted to Contain
Monoglyceride Citrate**

Bureau of Chemical Safety

Food Directorate

Health Products and Food Branch

**A PAHO/WHO Collaborating Center for
Food Contamination Monitoring**



November 2010



Canada 

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Purpose

This document provides information on Health Canada's proposal to amend the *Food and Drug Regulations* ("Regulations") to permit the food additive use of citric acid esters of mono- and diglycerides (synonymous names citric and fatty acid esters of glycerol, CAEM, CITREM) as an emulsifying agent in infant formulae for special medical purposes, specifically those that are based on crystalline amino acids or protein hydrolysates, or both.

Citric acid esters of mono- and diglycerides is a group of compounds, all of which contain a glycerol structure whose three hydroxyl groups are esterified with two to three moieties: at least one is esterified with citric acid, at least one with a fatty acid, and the third remains unesterified or is esterified with either citric acid or a fatty acid. The Regulations already permit the food additive use of monoglyceride citrate, which is a citric acid ester of monoglyceride whose fatty acid moiety is oleic acid. Because citric acid ester of mono- and diglycerides is considered to be a synonymous name for monoglyceride citrate, the Food Directorate has also considered enabling the use of citric acid esters of mono- and diglycerides in those foods where monoglyceride citrate is already permitted. In this regard, the proposed amendments would permit the use of citric acid esters of mono- and diglycerides as a class IV (antioxidant) preservative in fats and oils, lard, monoglycerides and diglycerides, shortening, in margarine, and in unstandardized foods (except unstandardized preparations of (a) meat and meat by-product (Divisions 14 and 21), (b) fish, and (c) poultry meat and poultry meat by-product). Citric acid esters of mono- and diglycerides would also be permitted for use as a carrier or solvent agent in natural extractives, spice extracts and in unstandardized flavouring preparations. As noted, citric acid esters of mono- and diglycerides would be permitted in unstandardized foods (with certain exceptions) as a class IV preservative. It is proposed that its possible use in unstandardized foods as an emulsifier also be recognized by listing it among other permitted emulsifying agents in the Regulations.

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 amendment of the Regulations or issuance of an [Interim Marketing Authorization](#).

Health Canada received a submission requesting that the Regulations be amended to permit the addition of citric acid esters of mono- and diglycerides (CITREM) in infant formulae for special medical purposes. Specialized formulae are required for infants with impaired metabolism, e.g.: infants suffering from certain food allergies and intolerances where whole protein cannot be tolerated; inborn error of metabolism - when the offending amino acid must be excluded (e.g.: phenylketonuria); or, conditions where the absorptive surface of the gut is damaged or impaired. Specialized infant formulae composed of mixtures of amino acids or hydrolyzed proteins, fat, carbohydrates and other nutritional elements are manufactured for infants with these types of conditions.

Citric acid esters of mono- and diglycerides fulfill the function of an emulsifier characterized by a high hydrophilic-lipophilic balance (HLB) value. This property is particularly useful in formulae containing hydrolyzed milk proteins or amino acids, which, unlike unhydrolyzed proteins, do not form protein emulsion. In such formulae, an adequate emulsifier is necessary in order to enable lipids and carbohydrates to uniformly disperse and prevent separation of the fatty phase or other formula components.

The advantage of citric acid esters of mono- and diglycerides lies in its potential to provide a complete replacement of a combination of three permitted emulsifiers: lecithin; diacetyl tartaric acid esters of mono- and diglycerides (DATEM); and mono- and diglycerides. The emulsifying properties of citric acid esters of mono- and diglycerides are greater than those of the three other additives combined. In addition, citric acid esters of mono- and diglycerides constitute a non-ionic substance that is able to withstand ionic interactions in formulae where numerous mineral and trace element ions are present; thus, it is particularly useful in its intended application.

The submission was specific to the proposed use of citric acid esters of mono- and diglycerides in infant formulae for special medical purposes. However, Health Canada's Food Directorate noted that a monoglyceride citrate is already permitted in a number of other foods. Monoglyceride citrate, being a citric acid ester of monoglyceride, belongs to the group, citric acid esters of mono- and diglycerides. Further, "citric acid esters of mono- and diglycerides" is a synonymous name for "monoglyceride citrate". Therefore, it is being proposed that amendments be made to add "citric acid esters of mono- and diglycerides" wherever "monoglyceride citrate" is permitted. Such a measure will help to improve consistency in the regulatory listings for this group of food additives.

Current Situation

Health Canada's Food Directorate has completed a safety assessment of citric acid esters of mono- and diglycerides when used as described in the submission, and has determined that there are no health or safety concerns with its addition to infant formulae that are based on protein hydrolysates or crystalline amino acids or both. Such specialized formulae are required for infants with impaired metabolism. Therefore, the department is proposing amendments to the Regulations to allow citric acid esters of mono- and diglycerides to be added to infant formulae based on crystalline amino acids or protein hydrolysates or both.

The company emphasized that 143 mg of the additive in 100 mL of the formula as consumed fulfills its intended technological (emulsifying) function. The proposed amendment of 155 mg per 100 mL of formula as consumed is slightly (less than 10%) above this level in order to accommodate future formulae developments foreseen for the Canadian market.

Health Canada's Food Directorate has also considered and identified no safety concerns with the proposed addition of citric acid esters of mono- and diglycerides to the tables in the Regulations where monoglyceride citrate (a citric acid ester of monoglyceride) is currently permitted. Monoglyceride citrate is a class IV preservative (antioxidant) approved for use in a variety of food products including margarine, shortening, lard and most unstandardized foods; also, it is permitted as a carrier or extraction solvent in spice extracts, natural extractives, and unstandardized flavouring preparations. Since the compositional standard for margarine that is outlined in the Regulations refers specifically to monoglyceride citrate, this standard would be amended accordingly by inclusion of citric acid esters of mono- and diglycerides. Further, the Food Directorate has not identified any safety issues with recognizing the potential function in unstandardized foods of citric acid esters of mono- and diglycerides as either a class IV preservative or an emulsifying agent.

Safety Assessment

Health Canada's Food Directorate scientists conducted a detailed and rigorous evaluation, focussed on safety and efficacy, of the submission for the use of citric acid esters of mono- and diglycerides in infant formulae for special medical purposes. The possible use of citric acid esters of mono- and diglycerides in those foods in which monoglyceride citrate is already permitted was also evaluated. Their evaluation considered chemical, toxicological and nutritional aspects of the proposed uses of citric acid esters of mono- and diglycerides, as described in the following sections.

Chemical Assessment

There may be several molecular formulae for citric acid esters of mono- and diglycerides. These glycerides are obtained through esterification of glycerol with citric and fatty acids or by reaction of a mixture of mono- and diglycerides of edible fatty acids with citric acid. Monoglyceride citrate, the food additive currently listed in the Regulations, is a mixture of glyceryl monooleate (ester with oleic acid) and its citric acid monoester. Therefore monoglyceride citrate belongs to the group of citric acid esters of mono- and diglycerides. Monoglyceride citrate has its own specifications outlined in both the latest, 7th edition of the Food Chemicals Codex (US Pharmacopeia, 2010-2011) and in the Joint World Health Organization/Food and Agriculture Organization of the United Nations Expert Committee on Food Additives (JECFA) [compendium of specifications for food additives](http://www.fao.org/ag/agn/jecfa-additives/search.html), available at <http://www.fao.org/ag/agn/jecfa-additives/search.html>

Specifications for citric acid esters of mono- and diglycerides are available in JECFA's compendium and those submitted by the petitioner meet JECFA's requirements. The latest edition of the Food Chemicals Codex (US Pharmacopeia, 2010-2011) does not currently provide specifications for this additive.

Toxicological Assessment and Dietary Exposure

Taking into account data on infant weight and formula intake (P.L. Pellet "Food energy requirements in humans", *Am. J. Clin. Nutr.*, 51, pp. 711-722, 1990; and M.J. Heinig et al., "Energy and protein intakes of breast-fed and formula-fed infants during the first year of life and their association with growth velocity: the DARLING Study", *Am. J. Clin. Nutr.*, 58, pp. 152-161, 1993) at the proposed level of 1550 ppm (mg/L) in ready-to-serve formula, the average intake of citric and fatty acid esters of glycerol (citric acid esters of mono- and diglycerides) in 3-month old infants would be 233.8 mg/kg b.w./day; in 6-month olds, 194.5 mg/kg b.w./day; and in 9-month olds, 138.8 mg/kg b.w./day.

The Joint World Health Organization/Food and Agriculture Organization of the United Nations Expert Committee on Food Additives (JECFA) evaluated this additive in 1973 and concluded that these esters are hydrolyzed completely in the intestinal tract into components which are normal constituents of the diet. Furthermore, the JECFA evaluation was based on knowledge of the metabolic fate and lack of toxicity of the constituent citric acid and fatty acid esters of glycerol. A "Not limited" acceptable daily intake (ADI) was attributed to this food additive. Such non-numerical ADIs are assigned to food additives for which no toxicological concerns are identified through their intended food additive uses.

The petitioner presented four clinical studies with groups of infants and young children. The liquid formula tested contained 95 mg of CITREM per 100 mL of the reconstituted liquid formula, administered for up to 13 weeks. These studies did not reveal any overt toxicity. However, the Food Directorate' scientists noted that, with the exception of one study, there was no extensive examination of the participating infants for signs of clinical toxicity.

An additional, fifth, clinical (unpublished) study was conducted for up to 20 weeks with ten infants affected by allergy to cow's milk. The reconstituted liquid formula contained 143.6 mg of the additive per 100 mL. The infants' plasma protein status and plasma amino acid profiles were assessed. These parameters were not adversely affected by the administered formula. Although, as in most of the previous studies, an extensive investigation was not conducted, overall, the study data were considered to be supportive of the safety in use of the product.

On the basis of the submitted data, JECFA's "not limited" ADI and the fact that this additive has been in use in infant formula in many other countries, Health Canada's scientists did not object to the proposed use of the additive in the reconstituted liquid formula at a level of 143.6 mg/100 mL, as consumed. Furthermore, no objection has been expressed to the petitioner's request for a maximum level of use of 155 mg/100 mL of the formula as consumed, which is less than 10% above that with no adverse effects demonstrated in the clinical trials.

Therefore, from a toxicological perspective, Health Canada scientists have no objections to the use of citric acid esters of mono- and diglycerides under the conditions of use proposed in the submission. Further, based on the "not limited" ADI, there would be no objections to enabling the use of this additive in those foods in which monoglyceride citrate is already permitted.

Nutritional Assessment

Health Canada's scientists reviewed the information provided and have not expressed any nutritional safety concerns for the proposed use of the additive in infant formula based on crystalline amino acids or protein hydrolysates, or both. Further, a safety review has raised no concerns with the proposed listing of "citric acid esters of mono- and diglycerides" wherever monoglyceride citrate (a citric acid ester of monoglyceride) is permitted in the Regulations.

Rationale for Action

- The information provided by the petitioner has satisfactorily met the requirements for a food additive submission outlined in Section B.16.002 of the Regulations. Citric acid esters of mono- and diglycerides will serve functionally as an emulsifier in infant formulae based on crystalline amino acids or protein hydrolysates or both. Therefore, it is proposed that citric acid esters of mono- and diglycerides be listed in Table IV of section B.16.100, Division 16 (Food Additives), Part B of the Regulations. Table IV contains a listing of those food additives that may be used as emulsifiers, gelling, stabilizing and thickening agents.

- In addition, the scientific information that was evaluated also supports the proposal to enable the use of citric acid esters of mono- and diglycerides in those foods to which monoglyceride citrate may already be added. Tables XI, Part IV (food additives that may be used as class IV preservatives) and Table XV of section B.16.100 (food additives that may be used as carriers or extraction solvents) would therefore be amended to include citric acid esters of mono- and diglycerides under similar conditions of use as monoglyceride citrate. Section B.09.016, which outlines the compositional standard for margarine, would be consequentially amended. The potential function in unstandardized foods of citric acid esters of mono- and diglycerides as either a class IV preservative or as an emulsifying agent would also be recognized by listing it for use in unstandardized foods under Table IV of section B.16.100 (food additives that may be used as emulsifying, gelling, stabilizing and thickening agents).

International Status

Citric and fatty acid esters of glycerol (citric acid esters of mono- and diglycerides) has been approved for use in infant formulae by other national jurisdictions. “Neocate”, an amino-acid based infant formula, is listed on the U.S. Food and Drug Administration inventory of exempt infant formulae; that is, formulae that are represented and labelled for use by infants with inborn errors of metabolism, or low birth weight or who otherwise have unusual medical or dietary problems. According to the petitioner’s information, the “Neocate” formula on the US market has contained citric acid esters of mono- and diglycerides at a level of 143 mg/100 mL as consumed since 2005. Furthermore, a GRAS Notice was issued in December 2007 for the use of this additive as an emulsifier in carbonated beverages at levels up to 563 mg/kg and in certain other food categories, including meat and poultry products, at levels up to 1125 mg/kg.

Food Standards Australia New Zealand (FSANZ) has listed citric and fatty acid esters of glycerol (citric acid esters of mono- and diglycerides) in formulae based upon protein substitutes (Clause 34, former 42 in Standard for Infant Formula Products, Proposal P 93). The additive is listed in Schedule 2 of the Food Additive Standard as an additive generally permitted at a level consistent with Good Manufacturing Practices in processed foods.

In the European Union (EU) member countries, citric and fatty acid esters of glycerol (citric acid esters of mono- and diglycerides) have been permitted for use for several years in general infant formulae (7500 mg/kg of formula sold as powder) and in formulae containing hydrolyzed proteins, peptides and amino acids (9000 mg/L of formula sold as liquid, which is much higher than the 1550 mg/L, or 155 mg/100 mL, proposed in this submission). The additive is also permitted in dietary foods for special medical purposes at the same levels (7500 mg/kg sold as powder and 9000 mg/L sold as liquid) for infants from birth onwards (European Parliament and Council Directive No. 95/2/EC of 20 February 1995, amended in 1997, 2003 and 2004).

The EU directive also allows the use of citric acid esters of mono- and diglycerides at the maximum level of 5000 mg/kg, singly or in combination with other mono- and diglycerides in baby foods, cereal-based foods and in biscuits and rusks for infants and young children in good health.

In the Codex Alimentarius General Standard for Food Additives (GSFA), citric and fatty acid esters of glycerol (citric acid esters of mono- and diglycerides) is listed in Table III of the Standard, that is, among additives that can be used in processed foods generally (except in foods listed in the Annex to Table III) at a level consistent with good manufacturing practice. Provisions for this additive in infant formula, infant formula for special medical purpose, follow-up formula and complementary foods for infants and young children have not yet been adopted but are being considered at advanced levels of the procedure.

Consultation

Manufacturers of margarine were informed through the Vegetable Oil Industry of Canada about the proposed amendment of the standard for margarine that would include citric acid esters of mono- and diglycerides among the list of additives that may be used as preservatives in margarine. They have not expressed any objection to this proposal.

Recommendations

It is recommended that a provision be included in Table IV, section B.16.100, Division 16, Part B of the Regulations to allow the use of 1550 mg of citric acid esters of mono- and diglycerides per litre of liquid, ready-to-serve (as consumed) formulae based on crystalline amino acids or protein hydrolysates or both (1550 mg/L is equivalent to 155 mg/100 mL and to 0.155%).

Furthermore, it is recommended that Tables XI (Part IV) and XV, Division 16, Part B of the Regulations be amended in order to introduce the item "Citric acid esters of mono- and diglycerides", which would be permitted in the same foods as listed for monoglyceride citrate and at the same levels as prescribed for monoglyceride citrate.

As noted previously, monoglyceride citrate is already permitted as a preservative in unstandardized foods (except unstandardized preparations of (a) meat and meat by-product (Divisions 14 and 21 of the Regulations), (b) fish, and (c) poultry meat and poultry meat by-product). Citric acid esters of mono- and diglycerides would be listed in Table XI, section B.16.100, as an alternative preservative in the same foods. Its possible use as an emulsifier, rather than as a preservative, in unstandardized foods would also be recognized by listing it in Table IV to section B.16.100.

Therefore, the proposed listing in Table IV, section B.16.100, Division 16, Part B of the Regulations may appear as follows:

Item No	Column I Additive	Column II Permitted in or upon	Column III Maximum level of use
	Citric acid esters of mono- and diglycerides	(1) Infant Formulae based on crystalline amino acids or protein hydrolysates, or both (2) Unstandardized foods	(1) 0.155% as consumed (2) Good manufacturing practice

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 “**Citric acid esters of mono- and diglycerides**” in the subject box of your e-mail. **Comments must be received by 12:00 a.m. EDT, January 31, 2010.**

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Additional Information

For more information on this initiative, please contact the [Chemical Health Hazard Assessment Division](#) at bcsc-bipc@hc-sc.gc.ca.

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