Scientific Literature Review Notice –March 14, 2014

Ceramides

Cosmetic Ingredient Review (CIR) procedures call for the development of a review of the available scientific literature for each cosmetic ingredient (and wherever appropriate, closely related ingredients), on the basis of the annual priority list. The Scientific Literature Review (SLR) shall consist of a bibliography of relevant scientific literature, study reports that have been submitted by interested parties, and a description of each literature reference or submitted study report.

For the group of ingredients that are referred to here as ceramides (full list of ingredients described below in Table 1), an intensive search of the published information on these ingredients has found insufficient information to justify preparation of a formal SLR. CIR, therefore, is issuing this SLR Notice to alert interested parties that a safety assessment is being prepared. Information found in the published literature was in the form of efficacy studies on the named cosmetic ingredients, efficacy studies of other cosmetic ingredients or pharmaceuticals where naturally occurring ceramide levels in the skin were evaluated, or data on a pseudo-ceramide (such as that found in an approved medical device) that is not a cosmetic ingredient. These studies were not relevant to the assessment of safety for the use of ceramide ingredients in cosmetics.

Generally, a ceramide is the amidation reaction product of a sphingoid base and a fatty acid.

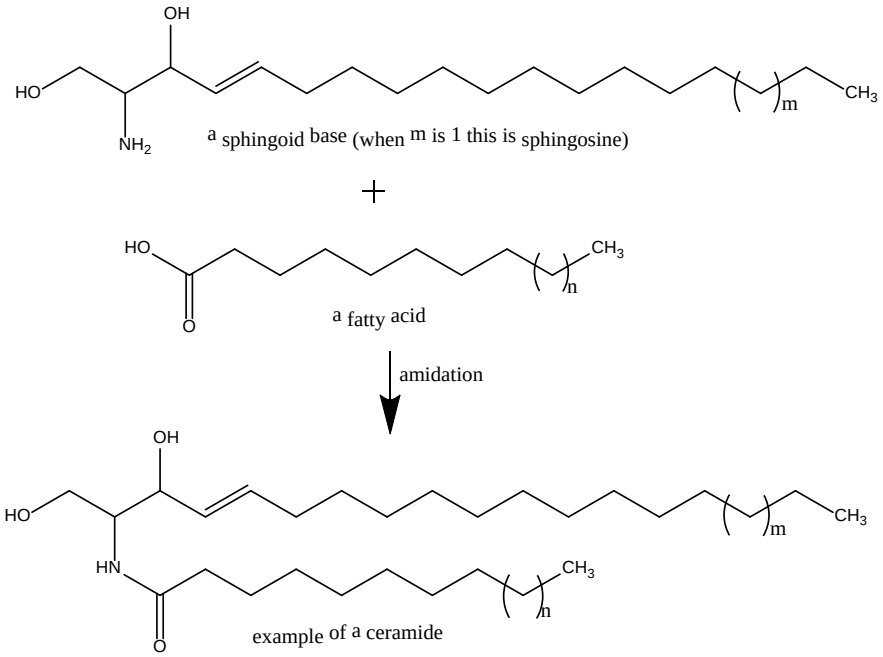


Figure 1. Example of a ceramide structure

The ingredients described herein vary principally by difference in chain lengths, of both the sphingoid and fatty acid residues, and the degree of unsaturation found in those chains. Additionally, these ingredients are each mixtures of ceramides, described in the detail available in Table 1.

In biological systems, ceramides are synthesized by de novo synthesis, sphingomyelin hydrolysis, or through a salvage pathway.[1] Ceramide manufacture could be accomplished by a variety of synthetic methods, but most methods revolve around amidation of a fatty acid with a sphingoid base.[2] This can be accomplished by reaction of the sphingoid base with an acyl chloride, but the results are not selective and esterification occurs concurrently with amidation. However, mild alkaline hydrolysis can be utilized to selectively remove the esters. Alternatively, activating the fatty acid with a carbodiimide results is ceramide synthesis without esterification.

A draft report will be reviewed at the **June 9-10, 2014** meeting of the CIR Expert Panel. If data are provided in response to this notice, those data will be incorporated into the draft report and reviewed by the Panel. All interested persons are provided 60 days from the date of this Notice to submit comments and/or additional published or unpublished data.* Given that this notice is issued because of a general absence of information, CIR is seeking information in a wide range of areas, including:

- Impurities data;
- Toxicokinetics data, specifically dermal absorption; if these ingredients were to have appreciable dermal absorption, oral animal toxicity data, including reproductive/developmental toxicity and carcinogenicity data, are needed, as are genotoxicity data; these data may not be crucial if these ingredients have no appreciable dermal penetration, however, if they were available, they would improve the resulting safety assessment;
- Oral, inhalation, and/or dermal toxicity data;
- Dermal, ocular, and/or other mucous membrane irritation and sensitization data; and
- Any other relevant safety information that may be available.

* Because all unpublished data submitted to CIR will be evaluated in public meetings and may be included in the final published safety assessment, CIR may not accept any confidential or proprietary data or information that cannot be made public. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. Please forward comments and data to Ivan Boyer, Senior Toxicologist, or Christina Burnett, Senior Scientific Analyst/Writer.

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[3]

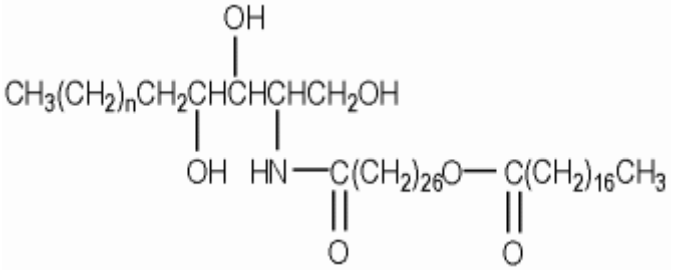
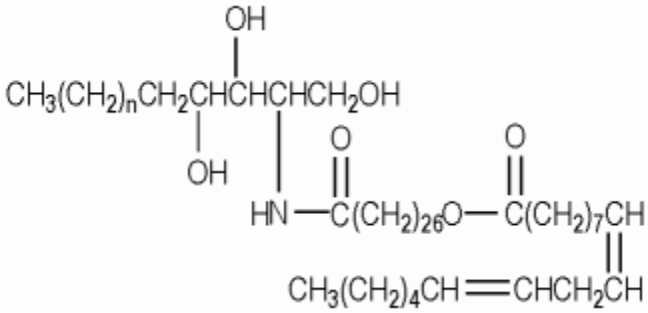
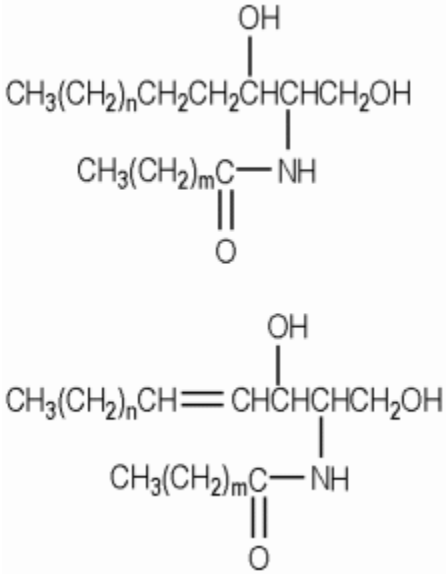
Ingredient CAS No.	Definition / Structure
Ceramide 1 100403-19-8	Ceramide 1 is the N-acylated phytosphingosine having the erythro structure that conforms generally to the formula:  where n has a value ranging from 10 to 20.
Ceramide 1A 100403-19-8	Ceramide 1 A is the N-acylated phytosphingosine having the erythro structure that conforms generally to the formula:  where n has a value ranging from 10 to 20.
Ceramide 2 100403-19-8	Ceramide 2 is the N-acylated sphingolipid having the erythro structure that conforms generally to the formulas:  where m has a value ranging from 14 to 28 and n has a value ranging from 10 to 16.

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[3]

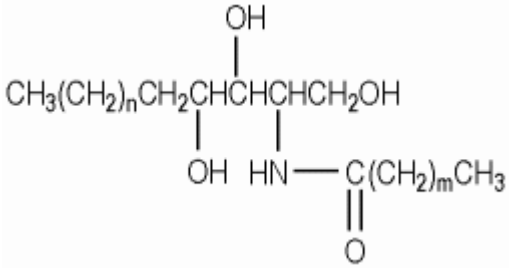
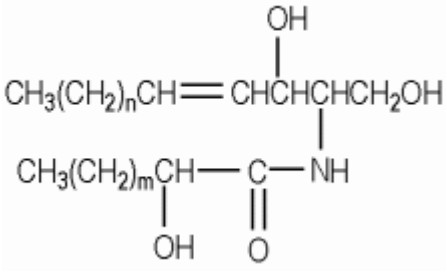
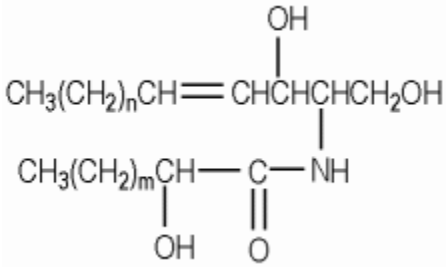
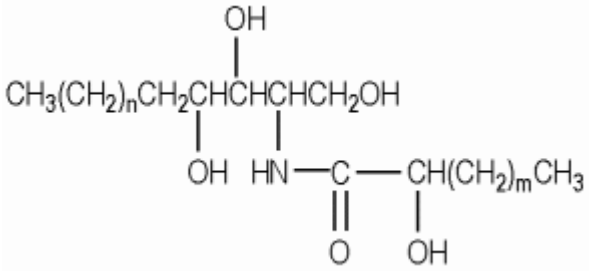
Ingredient CAS No.	Definition / Structure
Ceramide 3 100403-19-8 72968-43-5	Ceramide 3 is the N-acylated phytosphingosine having the erythro structure that conforms generally to the formula:  where m has a value ranging from 12 to 28 in which the acyl moiety may be saturated, mono-unsaturated, or di-unsaturated and n has a value ranging from 10 to 20.
Ceramide 4 100403-19-8	Ceramide 4 is the N-acylated sphingolipid having the erythro structure that conforms generally to the formula:  where m has a value ranging from 13 to 27 in which the acyl moiety may be saturated or mono-unsataurated and n has a value ranging from 10 to 16. Ceramide 4 is similar to Ceramide 5, however, the acylating hydroxy acids are generally shorter in Ceramide 4 than in Ceramide 5.
Ceramide 5 100403-19-8	Ceramide 5 is the N-acylated sphingolipid having the erythro structure that conforms generally to the formula:  where m has a value ranging from 13 to 27 in which the acyl moiety may be saturated or mono-unsatuarated and n has a value ranging from 10 to 16. Ceramide 5 is similar to Ceramide 4, however, the acylating hydroxy acids are generally longer in Ceramide 5 than in Ceramide 4.
Ceramide 6 II 100403-19-8	Ceramide 6 II is the N-acylated phytosphingosine having the erythro structure that conforms generally to the formula:  where m has a value ranging from 13 to 27 and n has a value ranging from 12 to 20.
Ceramide AP	Ceramide AP is the N-acylated sphingolipid consisting of Phytosphingosine having the D-erythro structure linked to an alpha-hydroxy saturated or unsaturated fatty acid.
Ceramide AS	Ceramide AS is the N-acylated sphingolipid consisting of sphingosine having the D-erythro structure linked to an alpha-hydroxy saturated or unsaturated fatty acid.
Ceramide EOP	Ceramide EOP is the N-acylated sphingolipid consisting of Phytosphingosine having the D-erythro structure linked to an esterified omega-hydroxy saturated or unsaturated fatty acid.

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[3]

Ingredient CAS No.	Definition / Structure
Ceramide EOS	Ceramide EOS is the N-acylated sphingolipid consisting of sphingosine having the D-erythro structure linked to an esterified omega-hydroxy saturated or unsaturated fatty acid.
Ceramide NP	Ceramide NP is the N-acylated sphingolipid consisting of Phytosphingosine having the D-erythro structure linked to normal saturated or unsaturated fatty acid.
Ceramide NS	Ceramide NS is the N-acylated sphingolipid consisting of sphingosine having the D-erythro structure linked to a normal saturated or unsaturated fatty acid.
Ceramide NS Dilaurate	Ceramide NS Dilaurate is the diester of Ceramide NS and lauric acid.

References

1. Elkhayat ES, Mohamed GA, and Ibrahim SRM. Activity and structure elucidation of ceramides. *Curr Bioact Compd*. 2012;8:370-409.

2. Hammarstrõm S. A convenient procedure for the synthesis of ceramides. *J Lipid Res.* 1971;12:760-765.

3. Gottschalck TE and Breslawec H. International Cosmetic Ingredient Dictionary and Handbook. Washington, DC: Personal Care Products Council, 2012.