Safety Assessment of Ceramides as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	February 20, 2015
Panel Meeting Date:	March 16-17, 2015

The 2015 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer, Ivan J. Boyer, Ph.D., Senior Toxicologist, and Bart Heldreth, Ph.D., Chemist.

1620 L Street, NW, Suite 1200 ◊ Washington, DC 20036-4702 ◊ ph 202.331.0651 ◊fax 202.331.0088
◊ cirinfo@cir-safety.org

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina Burnett, Senior Scientific Writer/Analyst
Date: February 20, 2015
Subject: Draft Final Safety Assessment of Ceramides

Enclosed is the draft Final Report of the Safety Assessment of Ceramides as Used in Cosmetics. (It is identified as *cerami032015rep* in the pdf document.)

At the December 2014 meeting, the Panel issued a tentative safety assessment on ceramides with the conclusion that the 23 ingredients listed in the report are safe in cosmetics in the present practices of use and concentration.

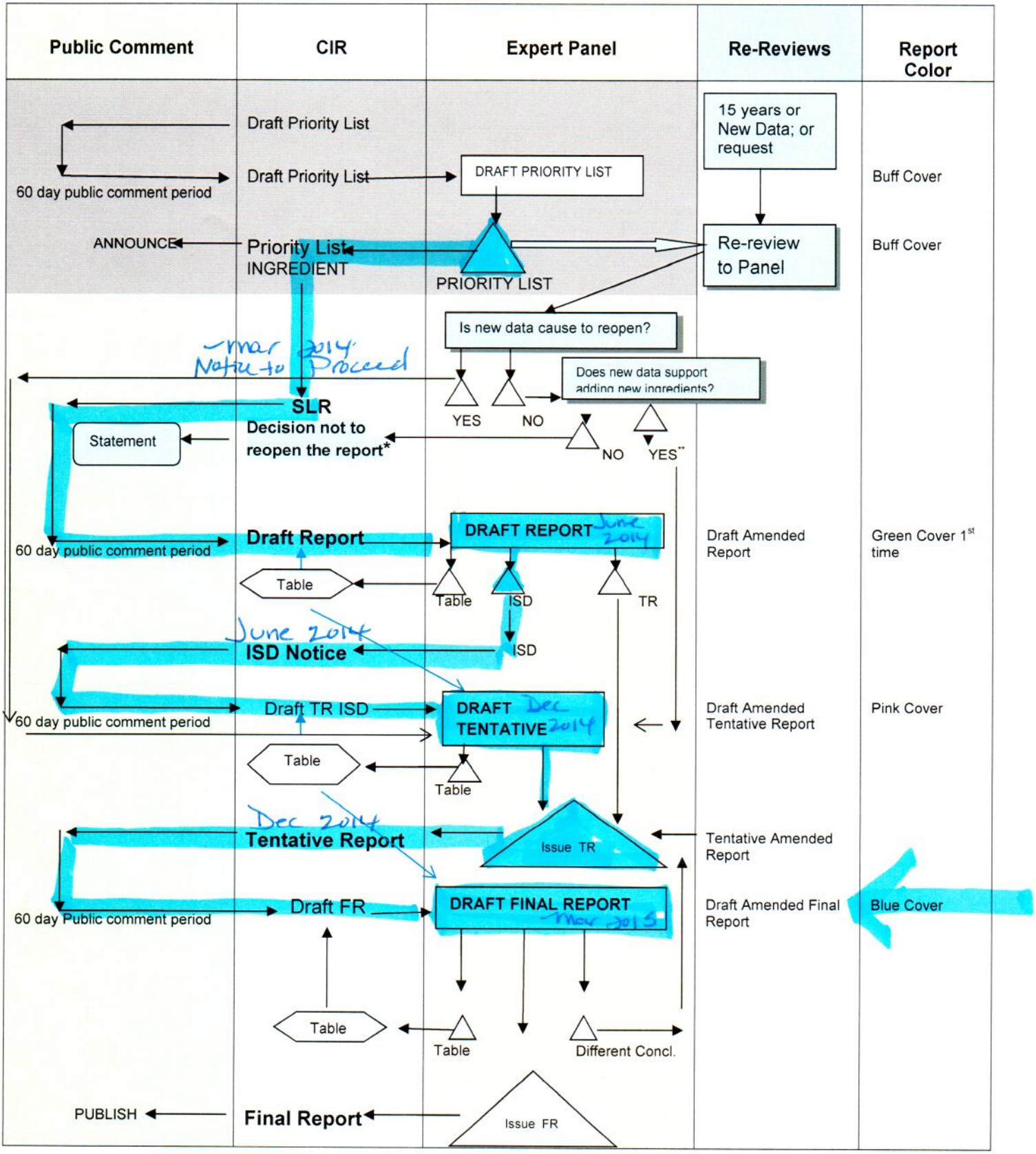
Since December, no new data have been received. Comments that were received from the Council prior to the December meeting, as well as those on the tentative safety assessment, have been considered (*cerami032015pcpc1* to *cerami032015pcpc3*). The comments are available for your review in this report package.

The Panel should carefully review the abstract, discussion, and conclusion of this report and issue a Final Safety Assessment.

Ceramides

SAFETY ASSESSMENT FLOW CHART

Mar 2015



Ceramides History

March 2014 – Scientific Literature Review Notice announced.

June 2014 - At the June 2014 CIR Panel Meeting, the Expert Panel requested additional data to support the safety of 15 ceramide ingredients. The additional data needs were: (1) methods of manufacture; (2) impurities; (3) concentrations of use of the ingredients added to this safety assessment; and (4) dermal absorption. If these ingredients exhibit appreciable dermal absorption, the additional data needed were (a) reproductive and developmental toxicity; (b) genotoxicity; and (c) dermal irritation and sensitization data at the highest maximum reported use concentration. The Panel also added 8 structurally similar ingredients to the ceramides report and expected that industry would provide safety test data that could be used to support read-across analysis for all of the ingredients in the report.

December 2014 - The Panel issued a tentative safety assessment for public comment with the conclusion that 23 ceramide ingredients are safe in cosmetics in the present practices of use and concentration: The Panel noted that there was a screening reproductive and developmental toxicity study on 2-Oleamido-1,3-Octadecanediol, however there was no data on carcinogenicity. The Panel considered the negative results of a reproductive and developmental toxicity study in rats and of in vitro genotoxicity assays, as well as the findings of no systemic toxicity at high doses in single and repeated oral dose animal studies, little to no irritation in ocular and dermal animal studies, no dermal irritation in human studies, and no dermal sensitization in multiple animal studies to support their conclusion for these ingredients.

The Panel also noted that the names of ceramide ingredients have changed recently. For example, the INCI name, Ceramide 1 has been retired and replaced by the name Ceramide EOP. For an interim period, products on the market may be labelled with either name, Ceramide 1 or Ceramide EOP, although both names refer to the same ingredient.

The Panel determined that these ceramide ingredients are safe as used, assuming that the ingredients are not derived from bovine central nervous system tissues.

Ceramides Data Profile – March 2015 – Writers, Christina Burnett, Ivan Boyer, and Bart Heldreth															
	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Tocikokinetics	Acute Toxicity	Repeated Dose Toxicity	Repro. /Develop. Toxicity	Genotoxicity	Carcinogenicity	Irritation/Sensitization - Animal	Irritation/Sensitization - Clinical	Ocular/Mucosal	Phototoxicity	Case Studies
Ceramide 1	X														
Ceramide 1A	X														
Ceramide 2	X	X	X	X		X			X		X	X	X		
Ceramide 3	X										X				
Ceramide 4															
Ceramide 5			X	X					X		X	X			
Ceramide 6 II	X														
Ceramide AP	X					X			X		X	X	X		
Ceramide AS															
Ceramide EOP	X														
Ceramide EOS	X														
Ceramide NP	X					X			X		X	X	X		
Ceramide NS	X														
Ceramide NS Dilaurate															
Ceramide NG															
Caprooyl Phytosphingosine	X														
Caprooyl Sphingosine	X														
Hydroxypalmitoyl Sphinganine	X		X			X			X		X		X		
2-Oleamido-1,3-Octadecanediol	X		X			X	X	X	X		X		X		
Caproyl Sphingosine															
Hydroxylauroyl Phytosphingosine															
Hydroxycapryloyl Phytosphingosine															
Hydroxycaproyl Phytosphingosine															

"X" indicates that data were available in the category for that ingredient.
Shaded cells indicate ingredients that have been previously reviewed by CIR.

Search Strategy for Ceramide Ingredients

- PubMed – February 18, 2014
  - Search for "ceramide dermal sensitization" – 1 hit, 1 ordered
  - Search for "ceramide dermal irritation" – 0 hits
- SciFinder – February 19, 2014
  - Search for "ceramides toxicity review. – 106 hits, 31 ordered
- SciFinder – February 21, 2014
  - Search ceramides by name/CAS#, limited search by document type, adverse effects – 184 hits, 24 ordered
- From reading review papers ordered – March 11, 2014
  - Search for potentially relevant citations – 24 selected, 24 ordered
- SciFinder – March 12, 2014
  - Search for "ceramides safety" – 29 hits, 1 obtained

Online Info

- COSMOS Database – March 12, 2014
  - Search for "ceramide" or "ceramides" studies/data – 0 hits
- European Chemicals Agency (ECHA) Database – March 12, 2014
  - Search for INCI names and available CASNs, and "ceramide" – 0 hits
- Internet (Google Search Engine) – March 12, 2014
  - Search for "ceramides medical devices" – 1 potentially relevant hit, downloaded
- eChemPortal (OECD) – March 12, 2014
  - Search for studies/data on "ceramides" – 0 hits
- INCI Dictionary/Cosmetics InfoBase – March 12, 2014
  - Search for studies/data on "ceramide" or "ceramides" – 0 hits
- U.S. EPA HPV List and ToxRef DB – March 12, 2014
  - Search for studies/data on "ceramide" or "ceramides" – 0 hits
- eCFR – March 12, 2014
  - Search for Code of Federal Regulations (CFR) notices – 1 hit, downloaded
- National Toxicology Program (NTP) Database – April 24, 2014
  - Search for studies on "ceramide"(all or part of chemical name) – 0 hits
- SCCS/SCCP – April 24, 2014
  - Search for "ceramide" – 0 hits
- Sigma Aldrich – April 24, 2014
  - Search for "ceramide" MSDSs – 0 hits
- National Library of Medicine (NLN) ToxNet Hazardous Substance Data Bank – April 24, 2014
  - Search for "ceramide" – 0 relevant hits
- Internet (Google Search Engine) – April 24, 2014
  - Search for "ceramide 4," "ceramide 5," "ceramide AS," and "ceramide NS"– 0 relevant hits
- PubMed – September 19, 2014
  - Search for "100403-19-8" OR "277-140-6" OR "309-560-3" OR "54422-45-6" OR "72968-43-5" OR "1,3,4-Octadecanetriol, 2-(2-Hydroxy)Dodecanamid" OR "1,3,4-Octadecanetriol, 2-(2-Hydroxy)Hexamide" OR "1,3,4-Octadecanetriol, 2-(2-Hydroxy)Octamide" OR "1,3,4-Octadecanetriol, 2-(2-Hydroxy)Stearamide" OR "1,3,4-Octadecanetriol, 2-Linolenoylheptacosamide" OR "1,3,4-Octadecanetriol, 2-Octadecanamide" OR "1,3,4-Octadecanetriol, 2-Stearoyloxyheptacosamide" OR "1,3-Hexadecanediol, 2-Hexadecanamide" OR "1-Stearoyl-C18-Sphingosine" OR "2-Oleamido-1,3-Octadecanediol" OR "9-Octadecenamide, N-[2-hydroxy-1-(hydroxymethyl)heptadecyl]-, (9Z)-" OR "Caprooyl Phytosphingosine" OR "Caprooyl Sphingosine" OR "Caproyl Sphingosine" OR Ceramide OR Ceramides OR "Ceramide 1" OR "Ceramide 1A" OR "Ceramide 2" OR "Ceramide 3" OR "Ceramide 4" OR "Ceramide 5" OR "Ceramide 6 11" OR "Ceramide 6 II" OR "Ceramide AP" OR "Ceramide AS" OR "Ceramide EOP" OR "Ceramide EOS" OR "Ceramide I" OR "Ceramide I A" OR "Ceramide NG" OR "Ceramide NP" OR "Ceramide NS" OR "Ceramide NS Dilaurate" OR "Hydroxycaproyl Phytosphingosine" OR "Hydroxycapryloyl Phytosphingosine" OR "Hydroxydodecanoyl-4-Hydroxysphinganine" OR "Hydroxydodecanoyl-C18-Phytosphingosine" OR "Hydroxyhexanoyl-4-Hydroxyshpinganine" OR "Hydroxyhexanoyl-C18-Phytosphingosine" OR "Hydroxyhexanoyl-Octadecane-1,3,4-Triol" OR "Hydroxylauroyl Phytosphingosine" OR "Hydroxyoctanoyl-4-Hydroxysphinganine" OR "Hydroxyoctanoyl-C18-Phytosphingosine" OR "Hydroxyoctanoyl-Octadecane-1,3,4-Triol" OR "Hydroxypalmitoyl Sphinganine" OR "Linoleoyloxyheptacosanoyl-4-Hydroxysphinganine" OR "Linoleoyloxyheptacosanoyl-C18-Phytosphingosine" OR "Palmitoyl-C16-Dihydrosphingosine" OR "Stearoyl-4-Hydroxysphinganine" OR "Stearoyl-C18-Phytosphingosine" OR "Stearoyloxyheptacosanoyl-4-Hydroxysphinganine" OR "Stearoyloxyheptacosanoyl-C18-Phytosphingosine" OR "α-Hydroxystearoyl-4-Hydroxysphinganine" OR "α-Hydroxystearoyl-C18-Phytosphingosine"

    AND

    1. (dermal OR skin OR (mucous AND membrane)) AND (irritation OR sensitization); 35 hits
    2. penetration OR (penetration AND enhancer); 131 hits
    3. toxicokinetics OR ADME OR absorption OR metabolism OR excretion; 18,291 hits
    4. "adverse health effects," 1 hit, not relevant

5. (repeated OR repeat) AND “dose toxicity,” 0 hits
6. neurotoxicity OR phototoxicity OR genotoxicity OR mutagenicity OR carcinogenicity OR “reproductive toxicity” OR “developmental toxicity” OR “reproductive and developmental toxicity” OR “acute toxicity” OR “subacute toxicity” OR “subchronic toxicity” OR “chronic toxicity,” 88 hits
7. “effects on the endocrine system,” 272 hits
8. “effects on the immune system,” 1,942 hits
9. “toxicity in vitro” OR “in vitro test,” 176 hits

20,936 hits, total; 14 ordered, 9 downloaded

- Scifinder – September 23, 2014
  - Ceramide or ceramides; 30,924 hits
    Hydroxypalmitoyl Sphinganine; 5 hits
    2-Oleamido-1,3-Octadecanediol; 8 hits
    Caprooyl Phytosphingosine; 1 hit
    Hydroxycaproyl Phytosphingosine; 0 hits
    Hydroxycapryloyl Phytosphingosine; 0 hits
    Hydroxylauroyl Photosphingosine; 0 hits
    Caprooyl Sphingosine; 1 hit
    Caproyl Sphingosine; 8 hits
    100403-19-8, 54422-45-6, 72968-43-5; 31 hits for all 3 CASNs
    277-140-6; 0 hits
    309-560-3; 0 hits

    Refine by (among other terms, as appropriate):

    1. Dermal irritation; 16 hits
    2. Sensitization; 1,739hits
    3. Dermal absorption; 8 hits
    4. Dermal penetration; 12 hits
    5. Penetration enhancer; 0 hits
    6. Toxicokinetics (absorption, distribution, metabolism, excretion) ; 1,264 hits
    7. Adverse health effects; 2 hits
    8. Repeated dose toxicity; 1 hit
    9. Neurotoxicity; 103 hits
    10. Phototoxicity; 12 hits
    11. Genotoxicity; 29 hits
    12. Mutagenicity; 205 hits
    13. Carcinogenicity; 2,449 hits
    14. Reproductive toxicity; 5 hits
    15. Developmental toxicity; 43 hits
    16. Acute toxicity; 31 hits
    17. Subacute toxicity; 1 hits
    18. Subchronic toxicity; 0 hits
    19. Chronic toxicity; 21 hits
    20. In vitro toxicity; 1 hit
    21. Manufacturing methods; 103 hits

  6,079 hits, total; 14 papers ordered, 2 papers downloaded; 4 patents of interest

Search updated on Pub Med January 22, 2015. No new relevant referenences.

Dr. Marks' Team December 8, 2014

DR. MARKS: Okay. So that means we are skipping forward to the ceramides, I believe; is that correct?

DR. SLAGA: Right.

DR. MARKS: Yes. Let me pull that up. So, in June we issued an insufficient data notice for the 15 ceramide ingredients in this report. Included method of manufacture, impurities, concentration of use, dermal absorption, FA exhibit, dermal absorption and the repro, and development of (inaudible) -- irritation studies. And then the panel also added structurally, similar ingredients, and so I'll start with what Ron Shank has to say; and then we'll go from there.

Ceramides, "If the chemists agree to read across with the ingredients in this report, then we can rely on the current data and the lack of penetration in the epidermis presumed, to say these ingredients are safe as used. Without read-across each ingredient will have to be considered individually, or limit the report to only those ingredients for which read-across is applicable."

DR. SLAGA: Basically that's what I'm saying, we have -- if you can read across you have methods of manufacturing, impurities, use data, genotoxicity, irritation sensitization, and therefore it's safe.

DR. MARKS: Yes.

DR. SLAGA: If you can read across.

DR. MARKS: And is a reason, with these ingredients you can't read across the way we've done with others?

DR. SLAGA: I thought you could. I do -- No concern there for me but --

DR. MARKS: Mm-hmm. So I'm not sure why Ron said the chemists say we can do this.

DR. BERGFELD: We don't need much --

DR. MARKS: Hmm?

DR. BERGFELD: He's trying to tell me us if we can read across. Can you read across?

DR. MARKS: Yes. So the 23 ingredients were okay. We have the data needs. Read across seems okay. I agree irritation sensitization. I had second tentative -- I called this the second tentative report because we had a tentative report before with safe as conclusion. But, Ron Hill, I haven't heard you speak yet.

DR. HILL: My take on this one, I guess, is unusual because we know ceramides have biology in the skin. But then we have a pretty good idea what they're doing there. Because we took out all the artificial ceramides and just went with ones that are in the range of naturally- present ceramides, I mean I think I made some statements last time about force feeding them. But yet my gut tells me there's really not a problem here with this group of compounds. And I don't think there's a real problem with read-across either.

DR. MARKS: Okay.

DR. HILL: So I think we are okay with this set now that we've taken out -- or never put in I guess, never included in the pseudoceramides in some of the ones that were being proposed for addition. And also because I re- reviewed something about what was known in the biology of the ceramides extracellularly in skin. I still think there are the molecules, some of these will be internalized into cells, so I was uncomfortable with some of the statements that were made. But nonetheless, I don't think that causes any issues in terms of safety.

DR. MARKS: So it seems like then we'll move forward, presumably I'm going to be seconding the report with the conclusion, a tentative report with conclusion, safe. I had a couple editorials, minor -- well somewhat editorial, minor. Christina? Oh, I'm sorry. Go ahead, Wilma.

DR. BERGFELD: I just want to ask Ron a question. I thought it was interesting in the metabolism, if they ingest such quantity that goes through all of the processing, (inaudible) of the liver, but it ends up in the skin. And if you put it on top of it, it ends up in the stratum corneum.

DR. SLAGA: Yes.

DR. HILL: Yes. Because we have a whole trafficking system for ceramides in the skin that it's crucial to maintaining the integrity of skin. And I mean, I guess I worry because we know there is specific biology. And I know a good bit more about ceramide biology because I've been working with a cancer stem cell guy who he is looking at ceramide, but really, ceramides are always giving us some beneficial effect when we use them in that way so --

DR. SLAGA: And then there was one animal study, one would expect that there some kind of a brain effect.

DR. BERGFELD: Yes. Yes.

DR. SLAGA: That shocked me too. The eyes and the skin versus -- to something, of course is a lot of (inaudible) in the brain too.

DR. HILL: So I feel uncomfortable. That's not really good enough to put in the discussion section that way, but --

DR. BERGFELD: So is it -- The comment that you made, which is common to a lot of these topical products, that at least have fatty acids in them, and ceramides and -- is the fact that they are biological. We all know that. So the question is, do they absorb, and do they have systemic behaviors?

DR. SLAGA: A very important context.

DR. HILL: I just think because of chemical nature of the compounds, the amounts that would actually make it out of the skin, to do anything systemically should be --

DR. BERGFELD: It would just be trapped in the skin. But the fact that you get it to GI tract and into the skin I thought was an easy router.

DR. BOYER: That's for a normal physiology; there are pathological conditions, diabetes for instance, even obesity where, you know, there's a disruption in the body's handling of ceramides. And so you can end up with some accumulation in the central nervous system, and other areas that can be problematic.

DR. MARKS: Okay. So a tentative report, safe.

DR. HILL: I did have one, what I consider to be a trivial question, which is, is caproyl with one O, the exact same compound as caprooyl with two Os? The structure is the same.

DR. BOYER: They shouldn't be.

DR. HILL: They are. And actually the -- Okay, yes, actually the CIS number that was given here in the table is also the same.

MS. BURNETT: Where are you?

DR. HILL: I'm on page 44 looking at the structures of the PDF.

MS. BURNETT: The generic has numbers that --

DR. HILL: Do you see which two I'm asking about?

MS. BURNETT: Yes. Yes.

DR. HILL: And also the phytosphingosine, I mean the fatty acid, which is what causes the caproyl, or caprooyl is the same in the structure. It's the ceramide part that changed -- well, actually the sphinganine part that changed there.

MS. BURNETT: I'll ask Bart and we'll have an answer for you tomorrow.

DR. HILL: I don't remember ever encountering the caprooyl with two O's before.

MS. BURNETT: Okay.

DR. HILL: That's why I'm asking the question.

MS. BURNETT: All right. I will ask him tomorrow since he prepared this table for us.

DR. MARKS: Okay.

MS. BURNETT: Are there any other discussions points you'd like?

DR. HILL: I feel like I haven't given you anything about your --

DR. BOYER: Have you edited the part that deals with signal-transduction role for ceramides and (inaudible) have you made some comments there, or --

DR. HILL: There is nothing I need to bring up here.

DR. BERGFELD: We do not have discussion for this ingredient, do we?

DR. HILL: Correct, that's why she's asking, is there anything more to capture.

DR. BERGFELD: Oh, I didn't hear -- have it under discussion.

DR. HILL: Because this is only the second meeting, we've looked at this, right, and we -- the last meeting was really focused heavily on what we include or not include.

DR. BERGFELD: You know, I think you should -- you should put in the discussion the read across.

DR. HILL: We need to put something pertinent.

DR. MARKS: Okay. Anything else?

DR. HILL: And I guess that, you know, the main point is that structures that we are proposing and reviewing the safety of here, fall well within the range of the naturally-occurring ceramides in the skin, and except for those genetic -- those individuals that are genetically compromised in the ceramide processing, we wouldn't expect any deleterious effects. And also the exposure from cosmetic uses should be low, except in the skin. And if that doesn't make sufficient sense, you can certainly ask me again in the morning.

DR. BERGFELD: Okay.

Dr. Belsito's Team December 8, 2014

DR. BELSITO: So I think we should have each of the CIR staff visit with us when this comes out to show us exactly how to use the wonderful capabilities of PDF. Maybe you can pay Dan to travel around and teach us all how to do it. (laughter) But it is wonderful. It's much quicker as you know all the functionalities. Okay, so I think that was it for report strategies, right? And I guess we don't move on to PEG cocamines. We move on to ceramides? So we're out of the admin. Let me save these changes.

Okay, so at our June meeting we requested additional data to support the 23 ceramide ingredients, that included methods of manufacture, impurities and dermal absorption. And if absorbed, data looking at repro and developmental toxicity, genotoxicity, dermal irritation and sensitization data for the highest maximum reported use concentration. And industry was going to provide us with safety data in concentration of use for eight structurally similar ingredients that we had tentatively agreed to add to the document.

Again, INCI is changing the name of some of these, and it's all very confusing. Some are getting two names, and two are getting one name and all these other things. But we've gotten a lot of substantial new data and not necessarily all exactly as we requested, but perhaps enough that we can come to some type of final conclusion at this meeting.

So there seem to be a extraction from neural tissue. So if that remains a concern, we would have to have our boiler plate about animal derived products and spongiform and cephalopathy. That was the first comment I had, where are the rest? But otherwise I thought it was pretty much probably safe, but I had some comments. That first of all, regarding the bovine or brain source, it was in Ivan's comment, but I don't see it mentioned in the document itself.

DR. ANSELL: No, we did get some manufacture -- methods of manufacture information and the extraction from animal tissues was not mentioned at all. That's why it doesn't appear in the report.

DR. BELSITO: So -- but where did you get it in your --

DR. ANSELL: From some published papers that indicated that one of the possible concerns of using ceremides as opposed to the pseudo ceramides, is that it can be derived from the central nervous system.

DR. BELSITO: So I guess we'd have to put that in a discussion, that it's our assumption that it's not, if we go ahead with that? And then under table three, its reported use in baby products, but no concentration for these baby products. I'm just pointing it out. I don't know if that concerns anyone. I mean, these are really going to sit on the stratum corneum. And lipid aerosol uses. That's the only comments I made. Otherwise I thought I was comfortable with the information we got.

DR. LIEBLER: Yeah, I thought this was actually quite good. I think most of our data needs have been met except for the dermal absorption. But I -- these compounds really aren't going to be significantly absorbed. The ones used in cosmetic ingredients are the longer chain compounds anyway. And even if there is any absorption, these things are already a major component of stratum corneum. And I thought

the overall tox profile was very clean. So relatively little reason for concern. And I thought that actually the -- on the first page of the introduction, PDF 32, the second paragraph after the list of compounds, does a really nice job of sort of developing a rationale to sort of explain away a lot of the irrelevant self-signalling literature that's not going to be applicable with these. So that's very nice.

DR. BELSITO: Right, and is "essentiality" a word, on that page? It says, "Many published reports address the essentiality." Like, essential nature or --

DR. LIEBLER: There we go. It's kind of like wonderfulness. (laughter)

DR. BELSITO: But that was it. So I thought we could go safe as used and it was except for the discussion that we're assuming cosmetic products are not derived from bovine neural tissue. Really no other significant discussion points from my standpoint.

DR. KLAASEN: I have a very small one. On the top page of 38, it says, "The supplier reported that." I would just remove that. Just those four words.

DR. BELSITO: Yeah, ceramides make up sphingomyelin. Everyone knows that.

DR. KLAASEN: Right.

MS. WEINTRAUB: Do you know what I'm going to say?

DR. LIEBLER: Of course (inaudible) I was about to say, I'm going to do a Rachel, but you beat me to it.

(laughter)

MS. WEINTRAUB: And it's my usual plus, your normal explanation for why it's okay.

DR. LIEBLER: So Rachel was going to point out that there are no carcinogenicity data. But I think that can be handled in the discussion, the genotoxic is over -- is completely negative with these and multiple assays and structure alerts.

MS. WEINTRAUB: There's also no mutagenicity data I believe.

DR. LIEBLER: That's the genotox. So they were not mutagenic in the Ames assay. It's just the title of that paragraph is genotoxicity, but includes mutagenicity and mammalian cell studies.

DR. SADRIEH: I was wondering if it will be useful to have a table in the report that says what kind of studies are available and whether they are adequate or not. So, you know, gene tox, carcinogenicity, sort of have it listed as a --

DR. LIEBLER: That's there.

DR. SADRIEH: It is there?

DR. LIEBLER: Yeah, that's a typical summary of the data.

DR. EISENMANN: It's part of the report package, but not actually in the physical report that will go to publication. So it should be at the beginning of the report package.

DR. KLAASEN: PDF 6.

DR. LIEBLER: This would be, like, supplemental data. It's available.

DR. KLAASEN: But if you look at PDF 6, it gives you a lot of that information of what data we have for which chemical. So just look up page 6.

DR. SADRIEH: Okay, I was just -- I mean, I was thinking for each chemical though. But if that's the way it is, then okay.

(background soft conversations - inaudible)

DR. BELSITO: So basically we're going with the safe as used and discussion that these are components of a normal stratum corneum, not expected to be absorbed. Tox state is pretty clean. There's no carcinogenicity data. The mutagenicity data is negative, and in the absence of any toxicologic concerns, our only other concern is that these should not be derived from bovine neural sources. Anything else?

Okay, so ceramides, we are done. Let me just save these. So we're going -- we also don't have repro and developmental. So again, that would be part of the discussion, the lack of absorption, the normal presence in the stratum corneum.

Full Panel Meeting December 9, 2014

DR. BELSITO: So, at the June 2014 meeting, we requested additional data to support the safety of the 23 ceramide ingredients and we asked for method of manufacture, impurities, dermal absorption, appreciable absorption, then additional data such as repro and developmental toxicity, geno toxicity, dermal irritation and sensitization data for the highest maximum reported use concentration, and industry was to have provided us with data and concentration, use data, and (inaudible) structurally similar ingredients that have been requested to be added to the report.

We're also dealing with this report with the fact that inky is in the process of changing names of these ceramides and -- somewhat confusing process, sometimes the one ceramide becomes just another different name, sometimes one ceramide becomes two different names or two different names are given to the same ceramide, so that's an issue that we sort of struggled with in this report.

We also -- there was a note that there could be some bovine neural sources for production of this, but we were -- this was not subsequently confirmed, but in the end, looking at all of the data that we did receive, we felt that we could go out with a "safe as used", in the discussion point out that although there was no carcinogenicity of reproductive, the element of toxicity data, the mutagenicity was negative. This is a component of the normal stratum corneum, has relative lack of absorption and looking at the individual molecules themselves, there were no other structural toxicologic concerns based upon structure, but also in the discussion to say that it's our understanding that these are not derived from bovine neural tissue, so we didn't need that usual caveat.

DR. BERGFELD: And that's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: And safe?

DR. BELSITO: Safe as used.

DR. BERGFELD: And no restrictions? Second?

DR. MARKS: Second.

DR. BERGFELD: Any further discussion regarding the conclusion or editorial? Ron?

DR. HILL: I raised the issue about two of the structures that looked the same in the dictionary and then what I realized later was that the problem is, although they are the same, the chemistry section is not at all clear that we have alternative stereochemistries for the ceramides and, in fact, some of those are a mixture of erythro-- yes, sir?

DR. HELDRETH: Christina brought this up to me and I think they are actually different. I think there might just be an error in the structure for (inaudible) because the (inaudible) standard for having (inaudible) oil as the acid residue is a 10-carbon chain, and (inaudible) oil is a 6-carbon chain.

DR. HILL: Well, I looked up the chemistry on that and capro (inaudible) is same number of carbons. They're both six carbons. The issue is, if you look up the ceramide literature, they're actually the same on the NA (inaudible) chain, but the stereochemistry of the (inaudible) is what's different. So, there's treo and there's erythro and some of these are actually mixtures of erythro and treo and were safety tested as such.

So, there's a -- I was trying to find the actual reference, but there's a really good reference in one of the chemical review journals that 2012 or 2013 references -- I'll send it to you -- that we're not capturing here, that takes through the chemistry of ceramides very thoroughly because the reality is, the fatty acid that's on the nitrogen can vary in our naturally occurring ceramides, the backbone can vary in terms of double bind, in terms of hydroxylation, and so common (inaudible), there are thousands and thousands of ceramides.

It doesn't change my conclusion, but I think we need to be sure that the chemistry section captures the reality of ceramides and we need to be very clear when the safety testing was done on a particular set of ceramides, which material is being evaluated.

Again, now that we're down to ceramides that are close analogues of naturally occurring ceramides, I have no issue with the safety or the conclusion, but that's part of the problem with what goes on in the dictionary because the stereochemistry is not indicated either in the name of the substance or in the stereochemistry that's written in the dictionary's structures, and that ultimately needs to be fixed, but right now it can put note in the usual fashion where you add to the dictionary entries to clarify what's going on.

But my online searching was is that caproyl and caprooyl actually have the same (inaudible) moiety and that what's different is the stereochemistry of the backbone if you look that up.

DR. HELDRETH: I don't disagree with the stereochemistry differences, but it is the typical pathway for the inky nomenclature committee to use caproyl, (inaudible).

DR. HILL: Well, we have caproyl and caprooyl, and that's different than what's here, because this is caprooyl and caprooyl -- two "o"s, double O, that's different than caproyl. So, let's just make sure we get all this right because (inaudible) --

DR. HELDRETH: -- one more time with this --

DR. HILL: -- (inaudible) we are, and then the stereochemistry, you know, where we can't change the dictionary entries in that table, we at least probably need a footnote so that we make clear -- because what the reader sees right now is the same structure and two different names, and even in one case the CAS number was duplicated, which is clearly an error, but that's --

DR. HELDRETH: Some of these CAS numbers are generic for the --

DR. HILL: Yeah, I think that's what the problem was --

DR. HELDRETH: So, that's why you're seeing that --

DR. HILL: And so they should be the same, and that adds to the confusion. But for the purposes of the report, we just -- we need to be sure we have a pretty good idea of what the safety testing was done on. In some cases, we may not, but at least if we -- we know they're mixtures, we know what's typically present. Again, it doesn't change my conclusion or (inaudible) or any of that. It's just --

DR. BERGFELD: Well, we take that into consideration and, I gather, fix it? Is that correct? Or change it if needed?

DR. HILL: And I think adding that it was a really thorough review of ceramides, and I'll send it to you, I know I have it on here but I'm not going to take the time to find it right now, it just takes you through the chemistry of these thousands of possible ceramides and there are a lot of controversy with which ones are prevalent in which tissues, there are a lot of conflicting results and it's because the analytical technology is just now coming to the place where some of this can be sorted out.

DR. BERGFELD: Well, thank you very much. Dan, do you want to comment on any of this?

DR. LIEBLER: I don't. Thanks.

DR. BERGFELD: Thank you. All right, well, we'll get that fixed if a fix is needed and make sure it's clear what has been tested, but we have a conclusion of safety. Any other discussion? Can we move forward then with an approval? All those in favor of a conclusion of safety? Thank you. So, that group of ingredients is approved, ceramides.

Safety Assessment of Ceramides as Used in Cosmetics

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The 2015 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer, Ivan J. Boyer, Ph.D., Senior Toxicologist, and Bart Heldreth, Ph.D., Chemist.

1620 L Street, NW, Suite 1200 ◊ Washington, DC 20036-4702 ◊ ph 202.331.0651 ◊fax 202.331.0088
◊ cirinfo@cir-safety.org

ABSTRACT

The Cosmetic Ingredient Review Expert Panel (Panel) reviewed the safety of ceramides, which function in cosmetics primarily as hair conditioning agents and skin conditioning agents-miscellaneous. The Panel considered relevant animal and human data related to these ingredients. The Panel concluded that ceramides were safe in cosmetics in the present practices of use and concentration described in this safety assessment:

INTRODUCTION

Ceramide ingredients function primarily as hair conditioning agents and skin conditioning agents-miscellaneous in cosmetics.[1] The 23 ingredients reviewed in this safety assessment are listed below:

ceramide 1
ceramide 2
ceramide 3
ceramide 4
ceramide 5
ceramide 1A
ceramide 6 II
ceramide AP
ceramide EOP
ceramide EOS
ceramide NP
ceramide NG
ceramide NS
ceramide AS
ceramide NS dilaurate
caprooyl phytosphingosine
caprooyl sphingosine
hydroxypalmitoyl sphinganine
2-oleamido-1,3-octadecanediol
caproyl sphingosine
hydroxylauroyl phytosphingosine
hydroxycapryloyl phytosphingosine
hydroxycaproyl phytosphingosine

Many of the reports found in the published literature presented efficacy studies on the named cosmetic ingredients, efficacy studies of other cosmetic ingredients or pharmaceuticals in which naturally-occurring ceramide levels in the skin were evaluated, and data on pseudo-ceramides (such as that found in an approved medical device; the chemical structures of which were determined by the Panel to be significantly different from those of the cosmetic ingredients addressed in this report). These studies were not relevant for assessing the safety of the ceramide ingredients included in this assessment. Additionally, a published paper that presents data from toxicology studies of several ceramides (1, 3, 3A, 3B, 6) and a phytosphingosine was reviewed, but the data from this paper were not incorporated into this report because some data points appeared to be merely cumulative to those of unpublished studies that were submitted by the Personal Care Products Council (Council) to the CIR, and the information presented in the paper is too incomplete to advance the development of a proper safety assessment.[2]

Many published reports address the essential nature of extracellular ceramides as components of the epidermal permeability barrier. These ceramides are clearly segregated to the extracellular spaces of the stratum corneum and other upper layers of the epidermis.[3,4] The family of ceramides that serve this function comprise about 50% of the lipid weight, and 5% of the total weight, of the stratum corneum.[4] Many other reports address the central role of ceramides in sphingolipid metabolism and the mediation of antiproliferative and proapoptotic functions inside cells, including keratinocytes. However, the extracellular barrier-forming ceramides are partly O-acylated molecules with long-chain fatty acids, in contrast to the signal-transducing ceramides.[3] Further, naturally-occurring ceramides are nearly cell-impermeant, and metabolic pathways can suppress intracellular ceramide accumulation to protect cells from ceramide-induced apoptosis and other effects. Thus, much of the extensive literature on the signal-transducing properties of ceramides does not appear to be relevant, and was not incorporated into this safety assessment report.

The names of ceramide ingredients changed during the development of this safety assessment. For instance the International Nomenclature Cosmetic Ingredient (INCI) name, Ceramide 1, which was originally assigned in 1997, has been retired. For an interim period, trade name assignments formerly published with the INCI name Ceramide 1 will be retained in the retired monograph, and also published with the new name assignment, Ceramide EOP. This means that, during the "interim period," products on the market may be labelled with either name, Ceramide 1 or Ceramide EOP, although both names refer to the same ingredient. Reported use data are associated primarily with the retired names. Likewise, most ingredient-specific data received for these ingredients may be associated with the retired INCI names. Accordingly, throughout this safety assessment report, the retired INCI names are used consistently to refer to the ingredients listed under either nomenclature. However, the data and the conclusions of the CIR Expert Panel will apply to these ingredients under both the new and the retired nomenclature.

The other name changes include (further explained in Table 1): Ceramide 2 will be replaced by two names, Ceramide NS (limited to sphingosine-based ceramides) and Ceramide NG (limited to sphinganine-based ceramides);

Ceramide 3 will be replaced by Ceramide NP; Ceramide 4 and Ceramide 5 will both be replaced by Ceramide AS; and Ceramide 6 II will be replaced by Ceramide AP.

Information on manufacturing methods for several ceramide ingredients submitted to CIR by the Council indicates that these ingredients are produced synthetically. Although some ceramides are plentiful in bovine central nervous system tissues (e.g., brain and spinal cord), the U.S. Food and Drug Administration (FDA) prohibits the use of ingredients derived from such tissues in cosmetic products because of the risk of transmitting infectious agents, such as bovine spongiform encephalitis (BSE) (21 CFR 700.27). Some ceramide ingredients may be derived from plant sources (e.g., those designated as phytosphingosines in the INCI names or definitions), which do not pose the risks associated with ingredient derived from the bovine central nervous system.[5]

CHEMISTRY

Definition and General Characterization

Generally, a ceramide is the amidation reaction product of a sphingoid base and a fatty acid (Figure 1).

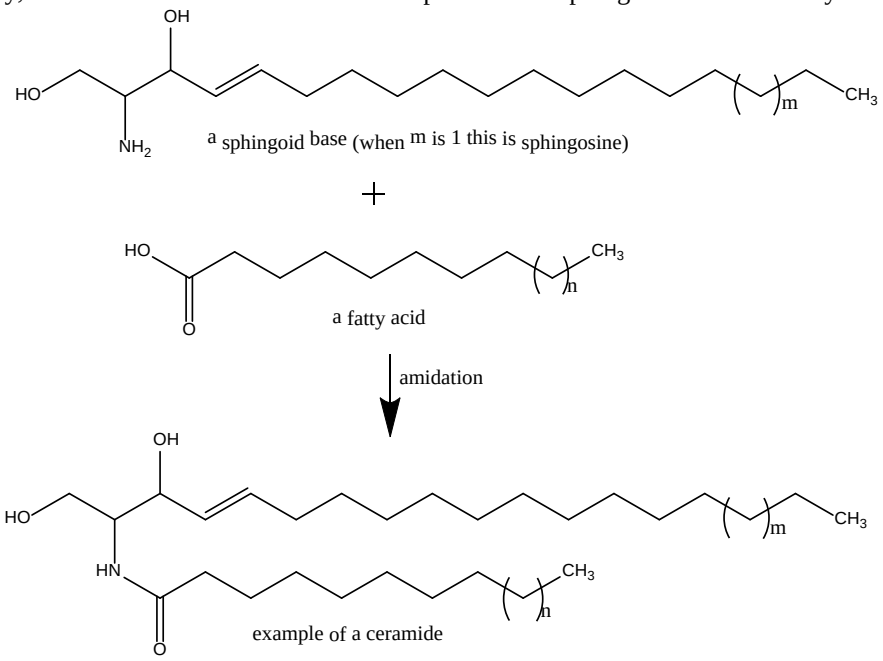

Figure 1. Example of a ceramide structure

The ceramide ingredients described herein vary principally in the chain lengths of the sphingoid and fatty acid residues and in the degree of unsaturation in the chains. The ceramide ingredients are also defined as having a certain stereochemistry related to the two stereocenters of the sphingoid base. Specifically, all of the ceramide ingredients, like those ceramides found in human skin, are defined as D-erythro. Additionally, each of these ingredients is a mixture of ceramides, described in more detail in Table 1. Chemical and physical properties were only available for ceramide 2: these data are presented in Table 2.

However, some of the ingredients in this report are not traditional ceramides and the stereochemistries therein are not defined. For example, the stereochemistries of hydroxypalmitoyl sphinganine and 2-oleamido-1,3-octadecanediol are not recited in the respective monographs.

Method of Manufacturing

In biological systems, ceramides are synthesized by de novo synthesis or sphingomyelin hydrolysis or through a salvage pathway.[6] Ceramide manufacture could be accomplished by a variety of synthetic methods, but most methods involve amidation of a fatty acid with a sphingoid base.[7] This can be accomplished by reaction of the sphingoid base with an acyl chloride, but the results are not selective and esterification and amidation occur concurrently. However, mild alkaline hydrolysis can selectively remove the esters. Alternatively, activating the fatty acid with a carbodiimide enables ceramide synthesis without esterification.

The unpublished data on method of manufacturing detailed below were received from suppliers of ceramide 2, ceramide 5, 2-oleamido-1,3-octadecanediol, and hydroxypalmitoyl sphinganine.

Ceramide 2

Ceramide 2 is produced synthetically via amide formation (i.e., reaction of (2S,3R)-sphinganine with methyl stearate to produce an amide), and other constituents/impurities are the isomers[8].

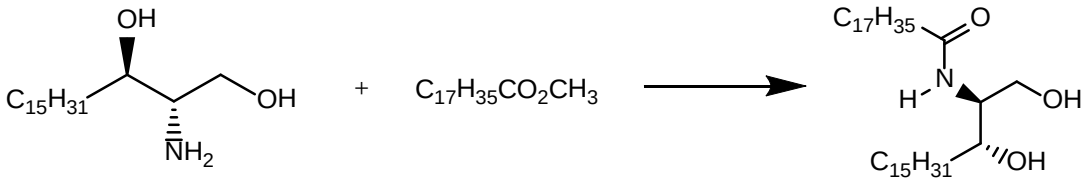

Figure 2. Formation of ceramide 2

It has been reported that ceramide 2 is a pure substance obtained by reacting a glycine ester derivative and activated palmitic acid before further reacting with stearoyl chloride.[9] Ceramide 2 is a mixture of D,L-erythro and D,L-threo with respective proportions of approximately 75% and 25%.

Ceramide 5

Ceramide 5 is produced synthetically via amide formation (i.e., reaction of (2S, 3R)-sphinganine) with methyl 2-hydroxyhexadecanoate to produce an amide. [10]

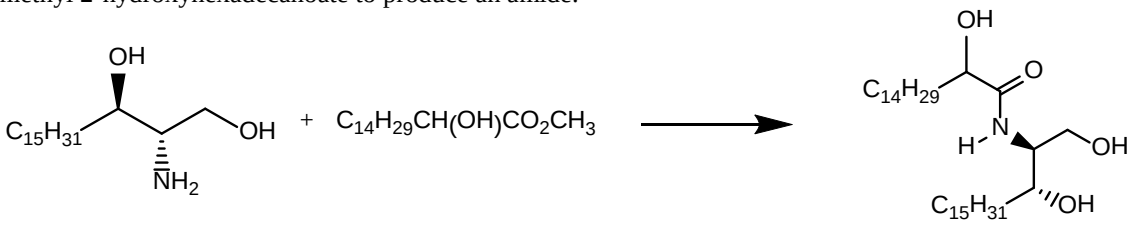

Figure 3. Formation of ceramide 5

2-Oleamido-1,3-Octadecanediol

2-Oleamido-1,3-octadecanediol is obtained by chemical reaction between dihydrosphingosine and an oleic acid derivative.[11]

Hydroxypalmitoyl Sphinganine

Hydroxypalmitoyl sphinganine is obtained by chemical reaction between dihydrosphingosine and a 2-bromohexadecanoic acid derivative, followed by the indirect substitution of bromine by hydroxyl group.[11]

Impurities

Ceramide 2

In a high performance liquid chromatography (HPLC) analysis of ceramide 2, only one peak was detected. No residual solvent was detected and the water content was less than 0.5% (no further details provided).[9]

A heavy metals analysis performed on ceramide 2 (reported under the new name ceramide NG) yielded the following results: lead < 10 ppm, arsenic < 3 ppm, mercury < 1 ppm, cadmium < 1 ppm, nickel < 1 ppm, and palladium < 1 ppm.[12]

Ceramide 5

The residue-on-ignition value for ceramide 5 was reported to be less than 0.5%.[10]

UV/VIS Absorption

Ceramide 2

The ultraviolet (UV) and visible (VIS) absorption spectra of solutions of ceramide 2 were measured with a Perkin Elmer Lambda 15 spectrophotometer.[13] Ceramide 2 was tested at concentrations of 0.001%, 0.01%, 0.1%,

and 1% in 95% ethanol or 1,4-dioxane. Negligible absorption was observed [***A***(300 nm) = 0.064 in ethanol and 0.078 in 1,4-dioxane] indicating that significant photochemical reactions in sunlight are unlikely.

USE

Cosmetic

The safety of the cosmetic ingredients included in this safety assessment is evaluated on the basis of the expected use in cosmetics. The Panel utilizes data received from the FDA and the cosmetics industry in determining the expected cosmetic use. The data received from the FDA are those it collects from manufacturers on the use of individual ingredients in cosmetics by cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP), and those from the cosmetic industry are submitted in response to a survey of the maximum reported use concentrations by category conducted by the Personal Care Products Council (Council).

According to the 2014 VCRP survey data, ceramide 3 is reported to be used in 359 formulations (Table 3). 2-Oleamido-1,3-octadecanediol is reported to be used in 352 formulations. The majority of the uses for all ceramide ingredients are in leave-on skin care preparations. The results of the concentration of use survey conducted by the Council in 2013 and 2014 indicate 2-oleamido-1,3-octadecanediol has the highest reported maximum concentration of use; it is used at up to 0.7% in hair conditioners. The highest maximum concentration of use reported for products resulting in leave-on dermal exposure is 0.2% in ceramide 2, ceramide 3, ceramide 6 II, ceramide AP, ceramide NP, and 2-Oleamido-1,3-octadecanediol in skin care preparations. Suppliers reported that ceramide 2 and ceramide 5 are used at concentrations up to 4% and 2%, respectively, in cosmetic products (no further details were provided).[8,10]

In some cases, no reported uses were received from the VCRP, but a maximum use concentration was provided in the industry survey. For example, ceramide 1A was not reported in the VCRP, but the industry survey indicated that it is used in leave-on formulations at concentrations up to 0.01%. It should be presumed that ceramide 1A is used in at least one cosmetic formulation.

Table 4 lists the eight ceramide ingredients not indicated to be in use based on the VCRP data and the results of the Council's concentration of use survey.

Some of these ingredients were reported to be used in hair sprays and body and hand or moisturizing sprays and could possibly be inhaled. For example, ceramide 3 was reported to be used in body and hand sprays at a maximum concentration of 0·001%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays.[17-20] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[18,19]

The ceramide ingredients in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[21]

TOXICOKINETICS

Ceramides are among the lipids that make up sphingomyelin, which is a major component of the lipid bilayer of the cell membranes of keratinocytes in the epidermis.[8,10] Ceramides are lipophilic and are likely to be readily absorbed into the skin. However, they are expected to remain in the stratum corneum and not penetrate any deeper.

The absorption, distribution and excretion of an analogous radiolabeled ceramide (palmitoyl D-erythro-sphingosine, [3–^{3}H]) was studied in male HWY rats.[22] The chemical structure of the ceramide tested, and the position of the radiolabel, were given as follows:

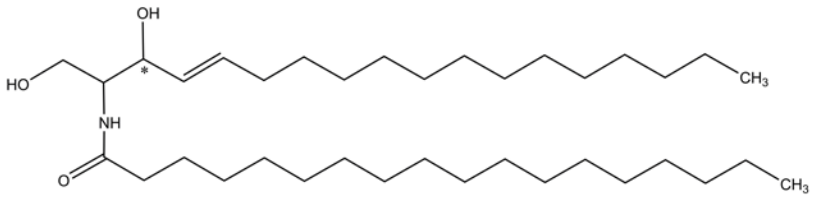

Figure 4. Ceramide analog

An unreported number of rats received a single oral administration (300 kBq/30 µg/kg) of ^{3}H-ceramide. Blood samples were serially collected from the subclavian vein at 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96 and 144 h and the

concentration of total radioactivity in the plasma was determined. Radioactivity was also measured in urine and feces collected up to 96 h post-treatment and in excised abdominal skin and carcass. Distribution of radioactivity was measured in selected organs and tissues up to 168 h post-treatment. The mean plasma concentration of radioactivity reached a maximum at approximately 10.67 h and then decreased with a half-life of 67.12 h. The mean cumulative excretion of radioactivity in urine and feces was approximately 4.79% and 87.44% of the dose, respectively. At 96 h after dosing, 1.67% and 3.67%, respectively, of the dose were still present in the skin and carcass. The radioactivity in the skin at 12 h was lower than that in plasma and the ratio of skin to plasma concentration was 0.7. However, at 120 h after dosing, the ratio of skin to plasma concentration increased to 4. An analysis of the distribution of radioactivity in a section of skin found radioactivity in the dermis and epidermis. At 72 and 168 h, the radioactivity in the epidermis was 5.6 % and 8.0%, respectively, of the radioactivity in skin, while at these same observation periods, the radioactivity in the dermis was 94.4% and 92.0%, respectively, of the radioactivity in skin. This study found that, following oral exposure, radiolabeled ceramide is distributed gradually in the dermis and then transferred to the epidermis.

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TOXICOLOGICAL STUDIES

Acute Toxicity

Acute oral and dermal toxicity studies are summarized in Table 5.[23-31] The median lethal oral dose (LD_{50}) was greater than 2000 mg/kg in rat studies of ceramide 2, ceramide AP, hydroxypalmitoyl sphinganine, and 2-oleamido-1,3-octadecanediol, and greater than 5000 mg/kg in rat studies of ceramide NP. In dermal studies on rats, the LD_{50}s were greater than 2000 mg/kg for ceramide NP, ceramide AP, and 2-oleamido-1,3-octadecanediol.

Repeated Dose Toxicity

Oral – Non-Human

2-Oleamido-1,3-Octadecanediol

The toxicity of 2-oleamido-1,3-octadecanediol was assessed in a 28-day oral study in groups of 5 male and 5 female Sprague-Dawley rats.[32] The rats received 10, 30, or 100 mg/kg of the test material in carboxymethylcellulose daily via gavage. An additional group of 5 males and 5 females received the vehicle alone as a control. The rats were observed weekly for clinical signs of toxicity and feed and water consumption. The rats were weighed twice weekly. Hematology, blood clinical chemistry, and urinalysis were also performed. Macroscopic and histologic examinations were performed at study end.

No mortalities were observed during the study. With the exception of the 30 mg/kg dose females, behavior, body weight gain, and feed consumption of the treated animals were comparable to those of the control animals. In the 30 mg/kg females, a slight decrease in body weight gain was observed. Decreased water consumption was observed during week 4 in the 10 mg/kg dose males and during week 2 to week 4 in the 30 mg/kg dose males. In the females, increased water consumption was observed in week 2 and week 3 in the 10 mg/kg dose group and during week 1 and week 2 in the 30 and 100 mg/kg dose groups. Mean white cell count in the 10 mg/kg dose females, mean neutrophils count in the 10 and 100 mg/kg dose males, and mean lymphocyte count in the 10 mg/kg dose females were statistically significantly lower than those of the controls, but individual results were within physiological ranges. Alanine transaminase and aspartate transaminase activities were high in one 100 mg/kg dose female, and a histopathological examination of the liver of this animal revealed a moderate single cell necrosis lesion with inflammatory cell infiltration. The mean urea level in the blood in the 30 mg/kg dose females was significantly lower than that of the controls, but individual results were within physiological ranges. No other statistically significant differences were observed in other hematologic and clinical chemistry parameters. Macroscopic examination found mean absolute weight of the heart in the 30 mg/kg dose males and mean relative weight of the heart in the 30 and 100 mg/kg dose males statistically significantly lower than those of the controls, but individual results were within normal physiological ranges. At 100 mg/kg in male rats, an increase in mean absolute and relative weight of the thymus was observed. Based on the findings in the thymus, the no observed effect level (NOEL) for 2-oleamido-1,3-octadecanediol was 30 mg/kg/day in rats.[32]

Dermal – Non-Human

2-Oleamido-1,3-Octadecanediol

The cutaneous tolerance of 2-oleamido-1,3-octadecanediol was tested in 3 male and 3 female Sprague-Dawley rats.[33] The animals received 1 g/kg body weight of test material in powder form applied to a 40 cm^2 area of the costal cutaneous area once daily for 14 consecutive days. Test sites were occluded for 6 h and then washed. An additional group of 3 male and 3 female rats that did not receive the powder served as control. The rats were

observed daily for clinical signs of toxicity, mortality, and cutaneous tolerance. The rats were weighed on days 7 and 14. Macroscopic and histologic examinations were performed at study end. No mortalities were observed during the study. Behavior and mean body weight gains of the treated animals were comparable to those of the control animals. No adverse reactions were observed in the skin. No macroscopic abnormalities of the skin or main abdominal and thoracic organs were observed. No treatment-related skin irritation was noted in the histological evaluation. It was concluded that the cutaneous tolerance of 1 g/kg 2-oleamido-1,3-octadecanediol in rats was good.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

2-Oleamido-1,3-Octadecanediol

The effects of 2-oleamido-1,3-octadecanediol on reproduction and development were studied in groups of 10 rats/sex/dose by oral gavage.[34] Dose levels tested were 0, 100, 300, and 1000 mg/kg body weight/day at a dose volume of 5 ml/kg body weight. The vehicle was a 0.5% aqueous solution of methylcellulose in purified water. Parental males were exposed to the test material 2 weeks prior to mating, during mating, and about 2 weeks post-mating (approximately 6 weeks total). Parental females were exposed 2 weeks prior to mating, during mating, during gestation, and during at least 4 days of lactation.

In the 1000 mg/kg dose group, one pregnant rat was observed with poor clinical condition and body weight loss toward the end of gestation and did not deliver by day 24 post-mating. Fibrinous and necrotic inflammation of the pericardium was observed microscopically. Another female in the high dose group was also observed with poor clinical condition from the end of gestation until day 2 post-partum. A normal delivery was observed in this rat, though, and no abnormal findings were observed at necropsy. The findings in these 2 high-dose females were not considered treatment-related. No treatment-related clinical effects were noted in the other animals in any dose group. No treatment-related effects were observed with mean body weights, mean feed consumption, or mating or fertility parameters (including mean numbers of corpora lutea, implantation sites per litter, pups delivered, and live pups).

Further, no increased incidences of mortality, adverse effects on body weight, influence on sex ratio, or treatment-related gross malformations were noted in the pups.

In the1000 mg/kg/day dose group, one parental male had several lesions in the urinary tract, including urinary lithiasis, thickened and red urinary bladder mucosa, and dilated right ureter and pelvic cavity of the right kidney. The researchers could not determine whether this finding was treatment-related or a random event. No other treatment-related effects were noted in parental animals at necropsy.

Based on the results of this study on 2-oleamido-1,3-octadecanediol, the researchers determined the maternal no observed adverse effect level (NOAEL) to be 1000 mg/kg body weight/day, and the NOEL for mating and fertility to be 1000 mg/kg body weight/day.[34]

GENOTOXICITY

In vitro genotoxicity studies are summarized in Table 6.[27-29,31,35-40] Ceramide 2, ceramide NP, ceramide 5, ceramide AP, hydroxypalmitoyl sphinganine, and 2-oleamido-1,3-octadecanediol were not mutagenic in Ames assays. Additionally, 2-oleamido-1,3-octadecanediol was not polyploidy-inducing or clastogenic in a metaphase chromosome analysis in Chinese hamster lung cells at a concentration up to 5000 μg/ml with and without metabolic activation.

CARCINOGENICITY

Data on carcinogenicity were not found in the published literature for ceramides, nor were unpublished data provided.

IRRITATION AND SENSITIZATION

Irritation

Ocular

Ocular irritation studies are summarized in Table 7.[27-29,31,41-44] Undiluted ceramide 2 was mildly irritating to rabbit eyes in one study, but not irritating in another. Ceramide NP, ceramide AP, and hydroxypalmitoyl sphinganine were also not irritating in rabbit eye studies when tested neat. 2-Oleamido-1,3-octadecanediol was slightly irritating when tested neat in rabbit eyes.

Dermal

Dermal irritation studies are summarized in Table 8.[27-29,31,45-52] In dermal studies, ceramide 2 (up to 5% in corn oil and undiluted), ceramide 3 (concentration not reported), ceramide 5 (up to 5% in white petrolatum), ceramide AP (undiluted), hydroxypalmitoyl sphinganine (undiluted), and 2-oleamido-1,3-octadecanediol (undiluted) were not irritating to rabbit or guinea pig skin. Slight irritation was observed in a dermal irritation study in rabbits with ceramide NP in propylene glycol, but no irritation was observed in other studies of the undiluted form. No dermal irritation was observed in human patch tests of ceramide 2 (up to 5% in lanolin), ceramide NP (up to 10% dispersion in Vaseline®), ceramide 5 (up to 5% in lanolin), and ceramide AP (5% dispersion in Vaseline®).

Sensitization

Dermal sensitization studies are summarized in Table 9.[27,31,53-55] Ceramide 2 (up to 20%), ceramide NP (up to 10%), ceramide 5 (up to 5%), and hydroxypalmitoyl sphinganine (up to 20%) were not sensitizing in guinea pig maximization tests.

SUMMARY

Ceramides function primarily as hair conditioning agents and skin conditioning agents-miscellaneous in personal care products. Naturally-occurring ceramides are normal constituents of the skin and are essential components of the epidermal permeability barrier.

Ceramide 3 has the most reported uses in cosmetics, with a total of 359; the majority of the uses are in leave-on skin care preparations. 2-Oleamido-1,3-octadecanediol has the second greatest number of overall uses reported, with a total of 352; the majority of those uses are also in leave-on skin care preparations.

In the Council's use-concentration survey, ceramide 3 was reported to have a maximum use concentration of 0.2%, which was reported in lipstick and face and neck skin care preparations. 2-Oleamido-1,3-octadecanediol had a maximum use concentration of 0.7% reported in hair conditioners.

Ceramides are among the lipids that make up sphingomyelin, which is a major component of the lipid bilayer that forms cell membranes of cells in the stratum corneum. Thus, ceramides are lipophilic and likely to be absorbed into the skin. However, they are expected to remain in the epidermis and not penetrate any deeper. An absorption, distribution and excretion study of an analogous radiolabeled ceramide in male rats found that, following oral exposure, the ceramide was distributed gradually to the dermis and then transferred to the epidermis.

The oral LD_{50} was greater than 2000 mg/kg in rat studies of ceramide 2, ceramide AP, hydroxypalmitoyl sphinganine, and 2-oleamido-1,3-octadecanediol, and greater than 5000 mg/kg in rat studies of ceramide NP. In dermal studies, the LD_{50} was greater than 2000 mg/kg in rats exposed to ceramide NP, ceramide AP, or 2-oleamido-1,3-octadecanediol.

In an oral repeated dose toxicity study, the NOEL for 2-oleamido-1,3-octadecanediol was 30 mg/kg/day in rats. At 100 mg/kg in male rats, an increase in mean absolute and relative weights of the thymus was observed. In a dermal repeated dose toxicity study, the cutaneous tolerance of 1 g/kg 2-oleamido-1,3-octadecanediol in rats was good. No skin reactions or systemic effects were observed

The maternal NOAEL and mating and fertility NOEL were both 1000 mg/kg body weight/day, respectively, in a rat reproduction and developmental study of 2-oleamido-1,3-octadecanediol. In the1000 mg/kg/day dose group, one male had several lesions in the urinary tract, including urinary lithiasis, thickened and red urinary bladder mucosa, and dilated right ureter and pelvic cavity of the right kidney. The researchers could not determine whether this finding was treatment-related or a random event. No other treatment-related effects were noted in parental animals. No increased incidences of mortality, adverse effects on body weight, influence on sex ratio, or treatment-related gross malformations were noted in the pups.

Ceramide 2, ceramide NP, ceramide 5, ceramide AP, hydroxypalmitoyl sphinganine, and 2-oleamido-1,3-octadecanediol were not mutagenic in Ames assays. Additionally, 2-oleamido-1,3-octadecanediol was not polyploidy-inducing or clastogenic in a metaphase chromosome analysis in Chinese hamster lung cells at concentrations up to 5000 μg/ml with and without metabolic activation.

Data on carcinogenicity were not found for ceramides in the published literature, nor were unpublished data provided.

Undiluted ceramide 2 was mildly irritating to rabbit eyes in one study, but not irritating in another. Ceramide NP, ceramide AP, and hydroxypalmitoyl sphinganine were also not irritating in rabbit eye studies when tested neat. 2-Oleamido-1,3-octadecanediol was slightly irritating when tested neat in rabbit eyes. In dermal studies, ceramide 2 (up to 5% in corn oil and undiluted), ceramide 3 (concentration not reported), ceramide 5 (up to 5% in white petrolatum), ceramide AP (undiluted), hydroxypalmitoyl sphinganine (undiluted), and 2-oleamido-1,3-octadecanediol (undiluted) were not irritating to rabbit or guinea pig skin. Slight irritation was observed in a dermal

irritation study in rabbits with ceramide NP in propylene glycol, but no irritation was observed in other dermal studies of the undiluted ingredient. No dermal irritation was observed in human patch tests of ceramide 2 (up to 5% in lanolin), ceramide NP (up to 10% Vaseline dispersion), ceramide 5 (up to 5% in lanolin), and ceramide AP (5% Vaseline dispersion).

Ceramide 2 (up to 20%), ceramide NP (up to 10%), ceramide 5 (up to 5%), and hydroxypalmitoyl sphinganine (up to 20%) were not sensitizing in guinea pig maximization tests.

DISCUSSION

The Panel considered the available data on ceramides and noted that there were no substantive data on reproductive and developmental toxicity or carcinogenicity. However, the Panel's concerns were reduced after reviewing the negative results of a reproductive and developmental toxicity study of 2-oleamido-1,3-octadecanediol in rats and of *in vitro* genotoxicity assays, as well as the findings of no systemic toxicity at high doses in single and repeated oral dose animal studies, little to no irritation in ocular and dermal animal studies, no dermal irritation in human studies, and no dermal sensitization in multiple animal studies. The Panel noted that ceramides with structures that were identical or very similar to the structures of these cosmetic ingredients exist naturally in the stratum corneum, and commented that the ceramides that are cosmetic ingredients would not be readily absorbed through the skin.

The Panel determined that these ceramide ingredients are safe as used, noting that ingredients derived from bovine central nervous system tissues are not permitted for use in cosmetic products.

The Panel discussed the issue of incidental inhalation exposure from hair sprays and body and hand or moisturizing sprays. There were no inhalation toxicity data available. The Panel considered pertinent data indicating that incidental inhalation exposures to ceramides in such cosmetic products would not cause adverse health effects, including data characterizing the potential for ceramides to cause systemic toxicity, ocular or dermal irritation or sensitization, and other effects. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that the following ceramide ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

ceramide 1
ceramide 2
ceramide 3
ceramide 4*
ceramide 5*
ceramide 1A
ceramide 6 II
ceramide AP
ceramide EOP
ceramide EOS
ceramide NP
ceramide NG*
ceramide NS
ceramide AS*
ceramide NS dilaurate*
caprooyl phytosphingosine
caprooyl sphingosine
hydroxypalmitoyl sphinganine
2-oleamido-1,3-octadecanediol
caproyl sphingosine*
hydroxylauroyl phytosphingosine*
hydroxycapryloyl phytosphingosine*
hydroxycaproyl phytosphingosine*

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

TABLES AND FIGURES

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

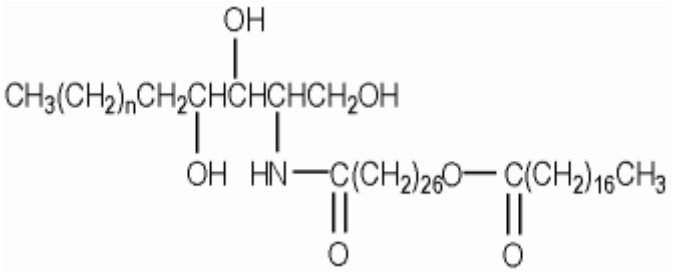
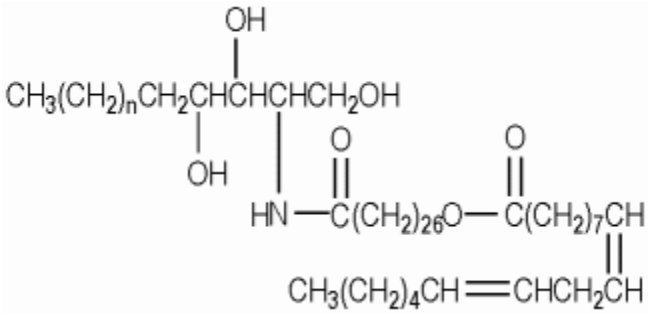
Ingredient CAS No.	Definition / Structure
Ceramide 1 (Retired) 100403-19-8	Ceramide 1 (Retired) is the *N*-acylated phytosphingosine having the erythro structure that conforms generally to the formula:  where n has a value ranging from 10 to 20. The INCI Name, Ceramide 1, originally developed in 1997, was designated with a retired status in 2014. For an interim period of time, trade name assignments formerly published with the INCI Name Ceramide 1 will be retained in the retired monograph, and also published with the new name assignment, **Ceramide EOP**. For further information, consult the Introduction, Retired INCI Names.
Ceramide 1A (Retired) 100403-19-8	Ceramide 1 A (Retired) 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. The INCI Name, Ceramide 1 A, originally developed in 1997, was designated with a retired status in 2014. For an interim period of time, trade name assignments formerly published with the INCI Name Ceramide 1 A will be retained in the retired monograph, and also published with the new name assignment, **Ceramide EOP**. For further information, consult the Introduction, Retired INCI Names.
Ceramide EOP	Ceramide EOP, formerly known under either of the INCI Names, Ceramide 1 or Ceramide 1 A, is the *N*-acylated sphingolipid consisting of Phytosphingosine having the D-erythro structure linked to an omega-hydroxy acid which is esterified with a saturated or unsaturated fatty acid.

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

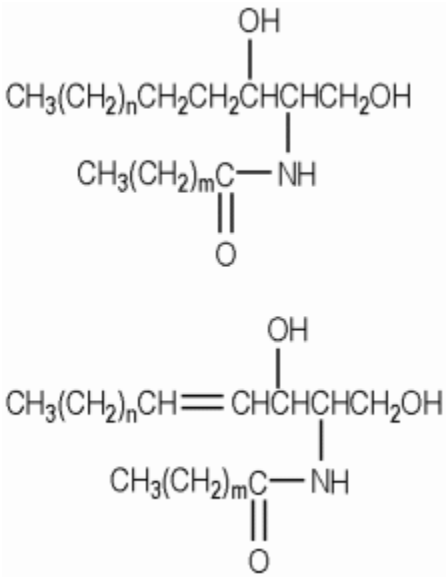
Ingredient CAS No.	Definition / Structure
Ceramide 2 (Retired) 100403-19-8	Ceramide 2 (Retired) is the *N*-acylated sphingolipid having the erythro structure that conforms generally to the formula:  where m has a value ranging from 14 to 28 and n has a value ranging from 10 to 16. The INCI Name, Ceramide 2, originally developed in 1997, was designated with a retired status in 2014. For an interim period of time, trade name assignments formerly published with the INCI Name Ceramide 2 will be retained in the retired monograph, and also published with the new name assignment as either **Ceramide NS or Ceramide NG**. For further information, consult the Introduction, Retired INCI Names.
Ceramide NS	Ceramide NS, formerly known under the INCI Name Ceramide 2, is the *N*-acylated sphingolipid consisting of sphingosine having the D-erythro structure linked to a normal saturated or unsaturated fatty acid. As opposed to the broader definition for Ceramide 2 which includes sphingolipids consisting of either sphingosine or dihydrosphingosine (sphinganine), Ceramide NS is limited to sphingosine-based ceramides.
Ceramide NG	Ceramide NG, formerly known under the INCI Name Ceramide 2, is the *N*-acylated sphingolipid consisting of Sphinganine having the D-erythro structure linked to a normal saturated or unsaturated fatty acid. As opposed to the broader definition for Ceramide 2 which includes sphingolipids consisting of either sphingosine or dihydrosphingosine (sphinganine), Ceramide NG is limited to sphinganine-based ceramides.

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

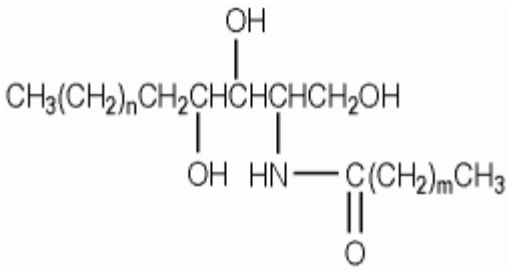
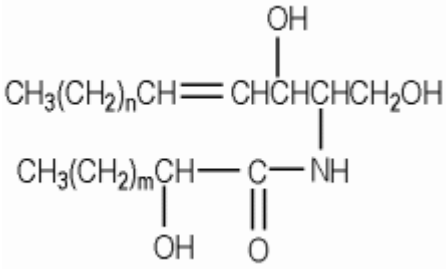
Ingredient CAS No.	Definition / Structure
Ceramide 3 (Retired) 100403-19-8 72968-43-5	Ceramide 3 (Retired) is the *N*-acylated phytosphingosine having the erythro structure that conforms generally to the formula:  where m has a value ranging from 12 to 28 in which the acyl moiety may be saturated, mono-unsaturated, or di-unsaturated and n has a value ranging from 10 to 20. The INCI Name, Ceramide 3, originally developed in 1997, was designated with a retired status in 2014. For an interim period of time, trade name assignments formerly published with the INCI Name Ceramide 3 will be retained in the retired monograph, and also published with the new name assignment, **Ceramide NP**. For further information, consult the Introduction, Retired INCI Names.
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 4 (Retired) 100403-19-8	Ceramide 4 (Retired) 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-unsaturated 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. The INCI Name, Ceramide 4, originally developed in 1997, was designated with a retired status in 2014. For an interim period of time, trade name assignments formerly published with the INCI Name Ceramide 4 will be retained in the retired monograph, and also published with the new name assignment, **Ceramide AS**. For further information, consult the Introduction, Retired INCI Names.

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

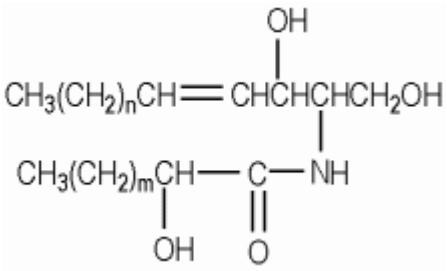
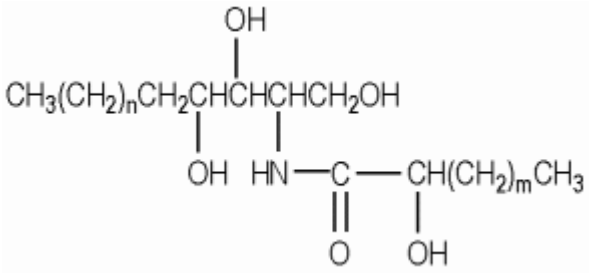
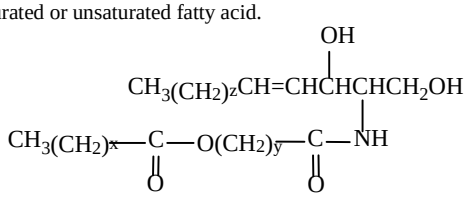
Ingredient CAS No.	Definition / Structure
Ceramide 5 (Retired) 100403-19-8	Ceramide 5 (Retired) is the *N*-acylated sphingolipid having the erythro structure that conforms generally to the formula:  where m has a value ranging from 13 to 27 in which the acyl moiety may be saturated or mono-unsaturated 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. The INCI Name, Ceramide 5, originally developed in 1997, was designated with a retired status in 2014. For an interim period of time, trade name assignments formerly published with the INCI Name Ceramide 5 will be retained in the retired monograph, and also published with the new name assignment, **Ceramide AS**. For further information, consult the Introduction, Retired INCI Names.
Ceramide AS	Ceramide AS, formerly known under either of the INCI Names, Ceramide 4 or Ceramide 5, is the *N*-acylated sphingolipid consisting of sphingosine having the D-erythro structure linked to an alpha-hydroxy saturated or unsaturated fatty acid.
Ceramide 6 II (Retired) 100403-19-8	Ceramide 6 II (Retired) 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. The INCI Name, Ceramide 6 II, originally developed in 1997, was designated with a retired status in 2014. For an interim period of time, trade name assignments formerly published with the INCI Name Ceramide 6 II will be retained in the retired monograph, and also published with the new name assignment, Ceramide AP. For further information, consult the Introduction, Retired INCI Names.
Ceramide AP	Ceramide AP, formerly known under the INCI name Ceramide 6 II, is the *N*-acylated sphingolipid consisting of Phytosphingosine having the D-erythro structure linked to an alpha-hydroxy saturated or unsaturated fatty acid.
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. 

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

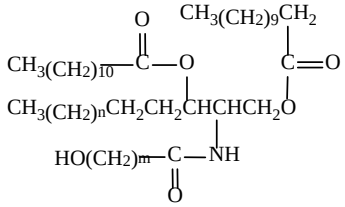
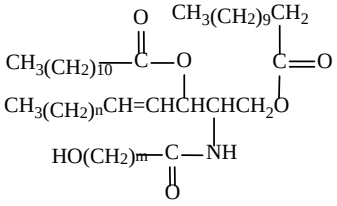
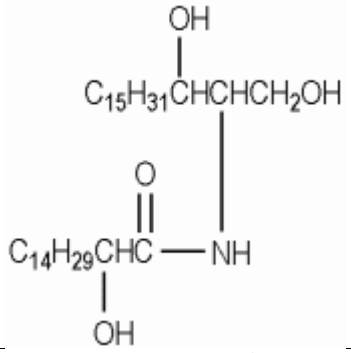
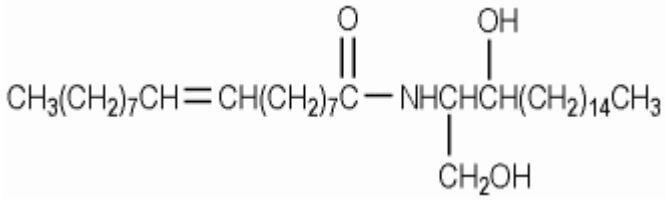
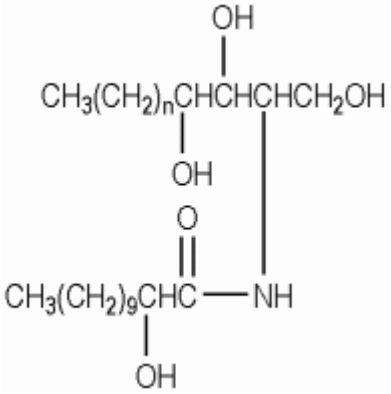
Ingredient CAS No.	Definition / Structure
Ceramide NS Dilaurate	Ceramide NS Dilaurate is the diester of Ceramide NS and lauric acid.  
Hydroxypalmitoyl Sphinganine	Hydroxypalmitoyl Sphinganine is the organic compound that conforms to the formula: 
2-Oleamido-1,3-Octadecanediol 54422-45-6	2-Oleamido-1,3-Octadecanediol is the organic compound that conforms to the formula: 
Hydroxylauroyl Phytosphingosine	Hydroxylauroyl Phytosphingosine is a synthetic *N*-acylated sphingolipid that conforms generally to the formula:  where n has a value ranging from 10 to 20.

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

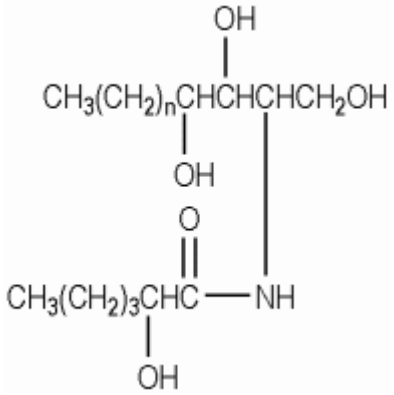
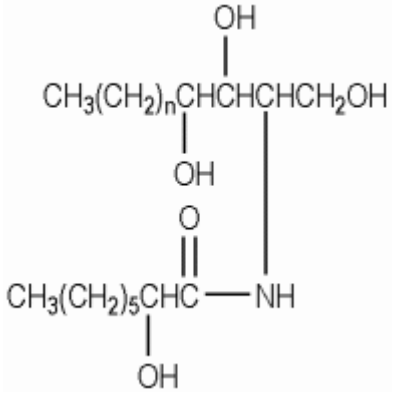
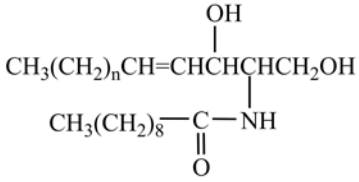
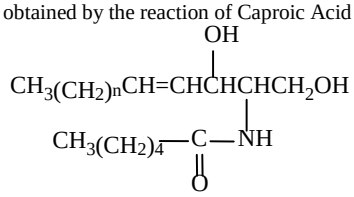
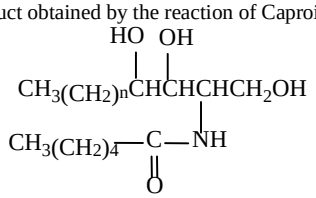
Ingredient CAS No.	Definition / Structure
Hydroxycaproyl Phytosphingosine	Hydroxycaproyl Phytosphingosine is a synthetic *N*-acylated sphingolipid that conforms generally to the formula:  where n has a value ranging from 10 to 20.
Hydroxycapryloyl Phytosphingosine	Hydroxycapryloyl Phytosphingosine is a synthetic *N*-acylated sphingolipid that conforms generally to the formula:  where n has a value from 10 to 20.
Caproyl Sphingosine 100403-19-8 (generic)	Caproyl Sphingosine is a synthetic *N*-acylated sphingolipid that conforms generally to the formula:  where n has a value of 10 to 16.
Caprooyl Sphingosine 100403-19-8 (generic)	Caprooyl Sphingosine is the product obtained by the reaction of Caproic Acid and sphingosine. 
Caprooyl Phytosphingosine	Caprooyl Phytosphingosine is the product obtained by the reaction of Caproic Acid and Phytosphingosine. 

Table 2. Chemical properties of ceramides

Property	**Value**	**Reference**
Ceramide 2		
Physical Form	Creamy white crystals	[56]
Molecular Weight g/mol	511.90	[56]
Melting Point ^{o}C	90.0-100.0	[56]
Flash Point ^{o}C	> 100	[56]

Table 3. Frequency (2014) and concentration of use (2013 and 2014) according to duration and type of exposure for ceramide ingredients.[14-16]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Ceramide 1		**Ceramide 2**		**Ceramide 3**		**Ceramide 1A**	
Totals[†]	**54**	**0.0000005-0.1**	**110**	**0.000005-0.2**	**359**	**0.00000001-0.2**	**NR**	**0.01**
Duration of Use								
Leave-On	48	0.0000005-0.1	99	*0.000005-0.2*	298	0.00000001-0.2	NR	0.01
Rinse Off	6	0.00001-0.00065	11	*0.0001-0.1*[c]	61	0.000001-0.013	NR	NR
Diluted for (Bath) Use	NR	NR	NR	*NR*	NR	NR	NR	NR
Exposure Type								
Eye Area	8	0.00002-0.00005	30	0.000005-0.2	29	0.002-0.05	NR	0.01
Incidental Ingestion	4	0.001	9	0.018-0.064	48	0.01-0.2	NR	NR
Incidental Inhalation-Spray	13[a]; 12[b]	0.00065	30[a]; 12[b]	0.0001; 0.01[a]	2; 109[a]; 63[b]	0.00000001-0.001	NR	NR
Incidental Inhalation-Powder	12[b]	0.0001	1; 12[b]	0.01	2; 63[b]; 2[d]	0.0001-0.01	NR	NR
Dermal Contact	47	0.0000005-0.045	86	0.000005-0.2	259	0.00005-0.2	NR	0.01
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.000325-0.00065	10	0.0001-0.01	48	0.00000001-0.013	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	0.1	NR	0.0004	NR	NR	NR	NR
Mucous Membrane	4	0.001	9	0.018-0.064	55	0.01-0.2	NR	NR
Baby Products	NR	NR	NR	NR	3	NR	NR	NR

	Ceramide AP		**Ceramide EOP**		**Ceramide EOS**		**Ceramide 6 II**	
Totals[†]	**14**	**0.00005-0.2**	**14**	**0.000001-0.01**	**14**	**0.01**	**52**	**0.00003-0.2**
Duration of Use								
Leave-On	14	0.00005-0.2	14	0.000001-0.01	14	0.01	48	0.00003-0.2
Rinse Off	NR	0.0005	NR	0.00001	NR	NR	4	0.0001-0.00065
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	1	0.0025-0.01	1	0.00005-0.01	1	NR	8	0.0025-0.01
Incidental Ingestion	NR	0.01	NR	0.001	NR	NR	4	0.01
Incidental Inhalation-Spray	2[a]; 11[b]	NR	2[a]; 11[b]	0.01	2[a]; 11[b]	0.01	12[a];12[b]	0.00003-0.00065
Incidental Inhalation-Powder	11[b]	0.01	11[b]	0.0001	11[b]	NR	12[b]	0.01
Dermal Contact	14	0.00005-0.2	14	0.000001-0.01	14	0.01	46	0.00003-0.2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	0.00033-0.00065
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.01	NR	0.001	NR	NR	4	0.01
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 3. Frequency (2014) and concentration of use (2013 and 2014) according to duration and type of exposure for ceramide ingredients.[14-16]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Ceramide NP		**Ceramide NS**		**Caprooyl Phytosphingosine**		**Caprooyl Sphingosine**	
Totals†	**16**	**0.00005-0.2**	**14**	**0.001-0.006**	**24**	**0.001**	**14**	**0.00033-0.00065**
Duration of Use								
Leave-On	16	0.00005-0.2	14	0.001-0.006	24	0.001	14	0.00065
Rinse Off	NR	0.0005-0.01	NR	0.001	NR	NR	NR	0.00033-0.00065
Diluted for (Bath) Use	NR	0.001	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	2	0.0025-0.005	1	NR	2	NR	1	NR
Incidental Ingestion	NR	0.2	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	2[a]; 11[b]	NR	2[a]; 11[b]	NR	2[a]; 12[b]	NR	2[a]; 11[b]	0.00065
Incidental Inhalation-Powder	11[b]	0.01	11[b]	NR	5; 12[b]	NR	11[b]	NR
Dermal Contact	16	0.00005-0.1	14	0.001-0.006	24	0.001	14	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	0.00033-0.00065
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.001-0.2	NR	NR	NR	NR	NR	NR
Baby Products	1	NR	NR	NR	NR	NR	NR	NR

	Hydroxypalmitoyl Sphinganine		**2-Oleamido-1,3-Octadecanediol**	
Totals†	**57**	**0.0025-0.062**	**352**	**0.01-0.7**
Duration of Use				
Leave-On	53	0.0025-0.062	241	0.01-0.2
Rinse Off	4	0.0025-0.0049	111	0.01-0.7
Diluted for (Bath) Use	NR	NR	NR	NR
Exposure Type				
Eye Area	5	0.0049	46	0.01-0.2
Incidental Ingestion	10	0.025	2	0.01
Incidental Inhalation-Spray	24[a]; 10[b]	NR	2; 43[a]; 7[b]	0.012-0.05; 0.05-0.1
Incidental Inhalation-Powder	10[b]	0.0025	7[b]	NR
Dermal Contact	47	0.0025-0.062	51	0.01-0.2
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	250	0.011-0.7
Hair-Coloring	NR	NR	6	0.01-0.1
Nail	NR	NR	NR	0.01-0.014
Mucous Membrane	10	0.025	2	0.01
Baby Products	NR	NR	NR	NR

NR = Not reported.

† Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a]. It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[b]. Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c]. 0.1% in a rinse-off "other" skin care preparation.

[d]. It is possible these products may be powders, but it is not specified whether the reported uses are powders.

Table 4. Ingredients that are not reported to be in use

Ceramide 4
Ceramide 5
Ceramide AS
Ceramide NG
Ceramide NS Dilaurate
Caproyl Sphingosine
Hydroxylauroyl Phytosphingosine
Hydroxycapryloyl Phytosphingosine
Hydroxycaproyl Phytosphingosine

Table 5. Acute toxicity studies.

Ingredient	Concentration/Dose	Animal System	Method	Results	Reference
		Oral			
Ceramide 2	0%, 5%, 10%, or 20% (w/v) (0, 500, 1000, or 2000 mg/kg) in olive oil; dose volume10 ml/kg.	5 male and 5 female Sprague-Dawley rats	Oral gavage	LD_{50} > 20% (2000 mg/kg) for both sexes; no mortalities; non-significant dose-dependent depression in body weight gain was observed in both males and females from 7 days post-administration; diarrhea was observed in some male and female rats in the 5% and 10% dose groups, but diarrhea was also observed in the control group and thus was attributed to the vehicle and not the test material; no other adverse effects observed	[30]
Ceramide 2	2000 mg/kg (no further details provided)	rats (no further details provided)	Oral	LD_{50} > 2000 mg/kg; no signs of toxicity observed	[31]
Ceramide NP	5000 mg/kg (no further details provided)	5 male and 5 female rats (strain not reported)	Oral gavage	LD_{50} > 5000 mg/kg; ataxia noted after each dosing; no other adverse effects observed	[23]
Ceramide NP	5000 mg/kg body weight in propylene glycol given as 2 dosages of 2500 mg/kg body weight within 24 h	5 male and 5 female Wistar rats	Oral gavage	LD_{50} > 5000 mg/kg; ataxia noted after each dosing; no other adverse effects observed	[27]
Ceramide NP	2000 mg/kg body weight in propylene glycol; dose volume 10 ml/kg body weight	2 male and 2 female Wistar rats	Oral gavage	LD_{50} > 2000 mg/kg; uncoordinated movement 2 and 4 h post-treatment in all animals; piloerection in 1 female 2 h post-treatment	[28]
Ceramide AP	2000 mg/kg body weight in propylene glycol; dose volume 10 ml/kg body weight	2 male and 2 female Wistar rats	Oral gavage	LD_{50} > 2000 mg/kg; uncoordinated movement 2 and 4 h post-treatment in all animals; hunched posture in 1 female 2 and 4 h post-treatment	[29]
Hydroxypalmitoyl Sphinganine	2000 mg/kg in methylcellulose; dose volume 10 ml/kg	5 male and 5 female Sprague-Dawley rats	Oral gavage	LD_{50} > 2000 mg/kg; body weight gain not affected by treatment; no mortalities; no abnormalities at necropsy	[25]
2-Oleamido-1,3-Octadecanediol	2000 mg/kg in 0.5% methylcellulose, dose volume 10 ml/kg	5 female Sprague-Dawley rats	Oral gavage	Maximal non-lethal dose was 2000 mg/kg; body weight gain slightly decreased in 2/5 animals during week 1 and 1/5 animals during week 2 but overall comparable to historical controls; no abnormalities at necropsy	[26]
		Dermal			
Ceramide NP	2000 mg/kg body weight in propylene glycol; dose volume 10 ml/kg body weight	2 male and 2 female Wistar rats	Dermal patch (no further details provided)	LD_{50} > 2000 mg/kg; body weight gain not affected by treatment; no mortalities; no adverse effects observed	[28]
Ceramide AP	2000 mg/kg body weight in propylene glycol	2 male and 2 female Wistar rats	Dermal patch for 24 h	LD_{50} > 2000 mg/kg; body weight gain not affected by treatment; no mortalities; no adverse effects observed	[29]
Ceramide AP	2000 mg/kg body weight in propylene glycol	2 male and 2 female Wistar rats	Dermal patch for 24 h	LD_{50} > 2000 mg/kg; body weight gain not affected by treatment; no mortalities; no adverse effects observed	[29]
2-Oleamido-1,3-Octadecanediol	2000 mg/kg	5 male and 5 female Sprague-Dawley rats	Dermal patch semi-occluded for 24 h	LD_{50} > 2000 mg/kg; body weight gain not affected by treatment; no mortalities; no abnormalities at necropsy	[24]

Table 6. Genotoxicity studies

Ingredient	Concentration/Dose	Method	Results	Reference
In Vitro				
Ceramide 2	0, 4.88, 19.5, 78.1, 313, 1250, or 5000 µg/plate with and without metabolic activation	Ames test in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA and 1537 and *Escherichia coli* strain wP2uvrA	Not mutagenic	[35]
Ceramide 2	50, 150, 500, or 1500 µg/plate with and without metabolic activation	Ames test in *S. typhimurium strains* TA 98, TA 100, TA 1535, and TA 1537	Not mutagenic	[36]
Ceramide 2	4.98-79.75 µg/plate (no further details provided)	Ames test in *S. typhimurium* (no further details provided)	Not mutagenic	[31]
Ceramide NP	100, 333, 1000, 3330, or 5000 µg/plate with and without metabolic activation	Ames test in *S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537	Not mutagenic	[27]
Ceramide NP	3, 10, 33, 100, 333, 1000, 3330, or 5000 µg/plate with and without metabolic activation	Ames test in *S. typhimurium* strains TA 98 and TA 100	Not mutagenic	[28]
Ceramide 5	Up to 5000 µg/plate with and without metabolic activation	Ames test in *S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 and in *E. coli* strain wP2uvrA	Not mutagenic	[37]
Ceramide AP	3, 10, 33, 100, 333, 1000, 3330, or 5000 µg/plate with and without metabolic activation	Ames test in *S. typhimurium* strains TA 98 and TA 100	Not mutagenic	[29]
Ceramide AP	3, 10, 33, 100, 333, 1000, 3330, or 5000 µg/plate with and without metabolic activation	Ames test in *S. typhimurium* strains TA 98 and TA 100	Not mutagenic	[29]
Hydroxypalmitoyl Sphinganine	25, 50, 100, 200, or 400 µg/plate with and without metabolic activation	Ames test in *S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 and in *E. coli* strain wP2uvrA	Not mutagenic	[38]
2-Oleamido-1,3-Octadecanediol	312.5, 625, 1250, 2500 or 5000 µg/plate with and without metabolic activation	Ames test in *S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 and in *E. coli* strain wP2uvrA	Not mutagenic	[39]
2-Oleamido-1,3-Octadecanediol	1250, 2500, or 5000 µg/ml with and without metabolic activation	Metaphase chromosome analysis in Chinese hamster lung cells; 3 treatment periods without metabolic activation consisted of a 6 h treatment with cell harvest 18 h later and 24 and 48 h treatments with immediate cell harvest after; 1 treatment period with metabolic activation consisted of a 6 h treatment with cell harvest 18 h later	No evidence of either polyploidy-inducing or clastogenic activity	[40]

Table 7. Non-human ocular irritation studies.

Ingredient	Concentration/Dose	Method	Results	Reference
Ceramide 2	100 mg undiluted	Eye irritation study in 3 rabbits (no further details provided)	No irritation	[31]
Ceramide 2	0.1 g undiluted	Eye irritation study in 6 male Japanese white rabbits; eyes washed in 3 rabbits 30 sec after treatment	Mildly irritating; all 3 rabbits in the non-washed group had mild discharge and moderate redness in the conjunctivae 1 h post-treatment, with slight chemosis in 1 animal, adverse effects disappeared by day 3 in two of the rabbits and by day 4 in the third; mild discharge in 2 rabbits and mild redness in 3 rabbits observed in conjunctivae of the washed group 1 h post-treatment, the discharge disappeared by day 1 post-treatment and all 3 animals were recovered by day 2; no other adverse effects were observed.	[44]
Ceramide NP	100 mg	Eye irritation study in New Zealand White rabbits; eyes assessed daily for 1 week post-treatment (no further details provided)	No irritation	[41]
Ceramide NP	27 mg (~ 0.1 ml) undiluted powder	Eye irritation study in 3 New Zealand White rabbits; test material instilled into conjunctival sac of one eye and rinsed after 24 h; reactions observed 1, 24, 48, and 72 h post-treatment	Not irritating; conjunctiva score of 1 in one rabbit at 1 and 48 h and 2 at 24 h; iris score of 1 in all rabbits at 1 h; chemosis score of 1 in one rabbit at 1 h; all effects reversed by 72 h (no further details provided)	[27]
Ceramide NP	51 mg (~ 0.1 ml) undiluted powder	Eye irritation study in 1 male New Zealand White rabbit; test material instilled into conjunctival sac of one eye for 24 h; reactions assessed 1, 24, 48, and 72 h post-treatment	Not irritating; conjunctiva score of 2 at 1 and 24 h and score of 1 at 48 h; iris score of 1 at 1 h; chemosis score of 2 at 1 h and score of 1 at 24 h; all effects reversed by 72 h (no further details provided)	[28]
Ceramide AP	51 mg (~ 0.1 ml) undiluted powder	Eye irritation study in 1 male New Zealand White rabbit; test material instilled into conjunctival sac of one eye for 24 h; reactions assessed 1, 24, 48, and 72 h post-treatment	Not irritating; conjunctiva score of 2 at 1 h and score of 1 at 24 h; chemosis score of 1 at 1 h; all effects reversed by 48 h (no further details provided)	[29]
Ceramide AP	64.7 mg (~ 0.1 ml) undiluted powder	Eye irritation study in 1 male New Zealand White rabbit; test material instilled into conjunctival sac of one eye for 24 h; reactions assessed 1, 24, 48, and 72 h post-treatment	Not irritating; conjunctiva score of 2 at 1 h and score of 1 at 24 and 48 h; chemosis score of 1 at 1 h; all effects reversed by 72 h (no further details provided)	[29]
Hydroxypalmitoyl Sphinganine	100 mg in powder form	Eye irritation study in 3 male New Zealand White rabbits; test material instilled into conjunctival sac of left eye; eyes not rinsed; reactions observed 1, 24, 48, and 72 h post-treatment	Not irritating; very slight or slight conjunctival inflammation observed 1 h post-treatment in 2/3 animals and for 48 h in the remaining animal; very slight corneal opacity noted 24 h post-treatment in the last animal; no reactions after 48 h in any animal	[42]
2-Oleamido-1,3-Octadecanediol	100 mg in powder form	Eye irritation study in 3 male New Zealand White rabbits; test material instilled into conjunctival sac of left eye; eyes not rinsed; reactions observed 1, 24, 48, and 72 h post-treatment	Slightly irritating; very slight to moderate conjunctival reactions (very slight to moderate chemosis, very slight or slight redness of the conjunctiva and discharge) were observed in all animals from day 1, with some reactions persisting up to day 8; iritis was noted in one animal on day 1	[43]

Table 8. Dermal irritation studies.

Ingredient	Concentration/Dose	Method	Results	Reference
		Non-Human		
Ceramide 2	2% or 5% in corn oil	Skin irritation study in 5 female Hartley/Dunkin albino guinea pigs; non-occluded patches (dose volume 0.02 ml, dose area 1.5 cm^2) on clipped, intact skin; patch sites assessed at 24 and 48 h post-application	Not irritating	51
Ceramide 2	undiluted	Acute dermal irritation study in 3 rabbits (no further details provided)	Not irritating	31
Ceramide 3	not reported	Skin irritation study in 6 male New Zealand White rabbits; semi-occluded patches on clipped skin for 24 h; patch sites assessed at 1, 24, 48, and 72 h post-patch removal	Not irritating	45
Ceramide NP	not reported	Skin irritation study in 6 male New Zealand White rabbits; semi-occluded patch on clipped intact skin for 24 h; patch sites assessed at 1, 24, 48, and 72 h post-patch removal	Not irritating	45
Ceramide NP	0.5 g, undiluted, powder form	Skin irritation study in 3 New Zealand White rabbits (sex not reported); semi-occluded patch (dose area 6 cm^2) on clipped intact skin for 4 h; patch sites assessed at 50 min, 24, 48, and 72 h post-patch removal	Not irritating	27
Ceramide NP	0.5 g in 0.8 ml of propylene glycol	Skin irritation study in 6 New Zealand White rabbits (sex not reported): semi-occluded patch (dose area 6 cm^2) on clipped intact skin for 4 h that was repeated on the same application sites for a total of 10 applications; patch sites assessed for up to 44 h after last patch	Slightly irritating; very slight or well defined erythema with or without very slight edema; no indication of enhancement of skin irritation after daily, repeated exposure to same skin-area and no signs of irreversible effects during the observation period	27
Ceramide NP	0.5 g, undiluted powder form	Skin irritation study in 1 male New Zealand White rabbit; semi-occluded patch on clipped, intact skin for 4 h; patch sites assessed at 1, 24, 48, and 72 h post-patch removal	Not irritating	28
Ceramide 5	2% or 5% in white petrolatum	Skin irritation study in 5 female Std:Hartley series albino guinea pigs; non-occluded patches (dose volume 0.02 ml, dose area 1.5 cm^2) on clipped, intact skin; patch sites assessed at 24 and 48 h post-application	Not irritating	52
Ceramide AP	0.5 g, undiluted powder form	Skin irritation study in 1 male New Zealand White rabbit; semi-occluded patch on clipped, intact skin for 4 h; patch sites assessed at 1, 24, 48, and 72 h post-patch removal	Not irritating	29
Hydroxypalmitoyl Sphinganine	undiluted powder form moistened with 0.5 ml distilled water	Skin irritation study in 3 male New Zealand White rabbits; semi-occluded (500 mg dose; dose area 6 cm^2) on clipped skin; patch sites assessed at 1, 24, 48, and 72 h post-patch removal	Very slight erythema in 2 animals on days 2 and 3; not irritating	46
2-Oleamido-1,3-Octadecanediol	undiluted powder form	Skin irritation study in 3 male New Zealand White rabbits; semi-occluded (500 mg dose) for up to 4 h on clipped skin; patch sites assessed at 1, 24, 48, and 72 h post-patch removal	Very slight erythema noted in 1 animal with a mean score of 0.7; not irritating	47

Table 8. Dermal irritation studies.

Ingredient	Concentration/Dose	Method	Results	Reference
		Human		
Ceramide 2	5% in lanolin	Human patch test in 43subjects; test material applied on upper arms with "TORII test plaster"; sites occluded for 24 h; sites assessed 2 and 24 h post-plaster removal	No dermal irritation	[50]
Ceramide 2	concentration not reported	Human patch test in 40 subjects; sites occluded for 24 h; 0.1 g on 17 cm diameter patch	No dermal irritation	[48]
Ceramide NP	10% Vaseline dispersion	Human patch test in 33 subjects; sites occluded for 24 h; sites assessed 1 and 24 h post-patch removal; 0.01 g in a Finn chamber	No dermal irritation	[27]
Ceramide NP	5% Vaseline solution	Human patch test in 44 subjects; sites occluded for 24 h; sites assessed 1 and 24 h post-patch removal; 0.01 g in a Finn chamber	No dermal irritation	[28]
Ceramide 5	3 % and 5% in lanolin	Human patch test in 43subjects; test material applied on upper arms with "TORII test plaster"; sites occluded for 24 h; sites assessed 2 and 24 h post-plaster removal	No dermal irritation	[49]
Ceramide AP	5% Vaseline solution	Human patch test in 44 subjects; sites occluded for 24 h; sites assessed 1 and 24 h post-patch removal; 0.01 g in a Finn chamber	No dermal irritation	[29]

Table 9. Non-human dermal sensitization studies.

Ingredient	Concentration	Method	Results	Reference
Ceramide 2	20% w/w	Skin sensitization test (Buehler test) in 10 male and 10 female guinea pigs with 5 male and 5 female control guinea pigs (no further details provided)	Not sensitizing	[31]
Ceramide 2	5% (w/w) for dermal induction; 2% and 5% for challenge; vehicle was corn oil	Guinea pig maximization test in 10 female Hartley/Dunkin albino guinea pigs; additional group of 10 received distilled water as control	Not sensitizing	[53]
Ceramide NP	5% (w/w) for intradermal induction; 25% (w/w) for dermal induction; and 2%, 5%, and 10% (w/w) for challenge; vehicle was propylene glycol	Guinea pig maximization test using 10 male and 10 female Himalayan albino guinea pigs for the test material	Not sensitizing	[27]
Ceramide 5	5% (w/w) for dermal induction; 2% and 5% for challenge; vehicle was white petrolatum	Guinea pig maximization test using 5 female Std: Hartley series albino guinea pigs; additional group of 2 guinea pigs were negative control	Not sensitizing	[54]
Hydroxypalmitoyl Sphinganine	2% (w/w)for intradermal induction, 20% (w/w) for dermal induction, 20% in challenge; vehicle was paraffin oil	Guinea pig maximization test using 10 male and 10 female Dunkin Hartley guinea pigs for the test material	Not sensitizing	[55]

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2014 FDA VCRP Raw Data

03D - Eye Lotion	CERAMIDE 1	5
03F - Mascara	CERAMIDE 1	3
07C - Foundations	CERAMIDE 1	3
07E - Lipstick	CERAMIDE 1	4
07G - Rouges	CERAMIDE 1	1
07I - Other Makeup Preparations	CERAMIDE 1	2
11A - Aftershave Lotion	CERAMIDE 1	1
11G - Other Shaving Preparation Products	CERAMIDE 1	2
12A - Cleansing	CERAMIDE 1	2
12C - Face and Neck (exc shave)	CERAMIDE 1	7
12D - Body and Hand (exc shave)	CERAMIDE 1	5
12F - Moisturizing	CERAMIDE 1	6
12G - Night	CERAMIDE 1	7
12H - Paste Masks (mud packs)	CERAMIDE 1	2
12J - Other Skin Care Preps	CERAMIDE 1	4
03A - Eyebrow Pencil	CERAMIDE 2	1
03B - Eyeliner	CERAMIDE 2	1
03C - Eye Shadow	CERAMIDE 2	4
03D - Eye Lotion	CERAMIDE 2	11
03F - Mascara	CERAMIDE 2	5
03G - Other Eye Makeup Preparations	CERAMIDE 2	8
05A - Hair Conditioner	CERAMIDE 2	1
05F - Shampoos (non-coloring)	CERAMIDE 2	7
05G - Tonics, Dressings, and Other Hair Grooming Aids	CERAMIDE 2	2
07A - Blushers (all types)	CERAMIDE 2	1
07B - Face Powders	CERAMIDE 2	1
07C - Foundations	CERAMIDE 2	5
07E - Lipstick	CERAMIDE 2	9
07I - Other Makeup Preparations	CERAMIDE 2	9
12A - Cleansing	CERAMIDE 2	2
12C - Face and Neck (exc shave)	CERAMIDE 2	12
12F - Moisturizing	CERAMIDE 2	21
12G - Night	CERAMIDE 2	7
12H - Paste Masks (mud packs)	CERAMIDE 2	1
12J - Other Skin Care Preps	CERAMIDE 2	2
01B - Baby Lotions, Oils, Powders, and Creams	CERAMIDE 3	2
01C - Other Baby Products	CERAMIDE 3	1
03B - Eyeliner	CERAMIDE 3	1
03C - Eye Shadow	CERAMIDE 3	6
03D - Eye Lotion	CERAMIDE 3	8
03F - Mascara	CERAMIDE 3	4
03G - Other Eye Makeup Preparations	CERAMIDE 3	10
04E - Other Fragrance Preparation	CERAMIDE 3	1

05A - Hair Conditioner	CERAMIDE 3	15
05B - Hair Spray (aerosol fixatives)	CERAMIDE 3	1
05E - Rinses (non-coloring)	CERAMIDE 3	2
05F - Shampoos (non-coloring)	CERAMIDE 3	15
05G - Tonics, Dressings, and Other Hair Grooming Aids	CERAMIDE 3	11
05I - Other Hair Preparations	CERAMIDE 3	4
07B - Face Powders	CERAMIDE 3	2
07C - Foundations	CERAMIDE 3	14
07E - Lipstick	CERAMIDE 3	48
07G - Rouges	CERAMIDE 3	1
07I - Other Makeup Preparations	CERAMIDE 3	8
10A - Bath Soaps and Detergents	CERAMIDE 3	3
10E - Other Personal Cleanliness Products	CERAMIDE 3	4
11A - Aftershave Lotion	CERAMIDE 3	1
11E - Shaving Cream	CERAMIDE 3	2
11G - Other Shaving Preparation Products	CERAMIDE 3	2
12A - Cleansing	CERAMIDE 3	12
12C - Face and Neck (exc shave)	CERAMIDE 3	50
12D - Body and Hand (exc shave)	CERAMIDE 3	13
12F - Moisturizing	CERAMIDE 3	69
12G - Night	CERAMIDE 3	22
12H - Paste Masks (mud packs)	CERAMIDE 3	6
12I - Skin Fresheners	CERAMIDE 3	3
12J - Other Skin Care Preps	CERAMIDE 3	14
13A - Suntan Gels, Creams, and Liquids	CERAMIDE 3	4
03D - Eye Lotion	CERAMIDE 6 II	6
03F - Mascara	CERAMIDE 6 II	2
07C - Foundations	CERAMIDE 6 II	3
07E - Lipstick	CERAMIDE 6 II	4
07G - Rouges	CERAMIDE 6 II	1
07I - Other Makeup Preparations	CERAMIDE 6 II	2
11A - Aftershave Lotion	CERAMIDE 6 II	1
11G - Other Shaving Preparation Products	CERAMIDE 6 II	2
12A - Cleansing	CERAMIDE 6 II	1
12C - Face and Neck (exc shave)	CERAMIDE 6 II	9
12D - Body and Hand (exc shave)	CERAMIDE 6 II	3
12F - Moisturizing	CERAMIDE 6 II	5
12G - Night	CERAMIDE 6 II	7
12H - Paste Masks (mud packs)	CERAMIDE 6 II	1
12J - Other Skin Care Preps	CERAMIDE 6 II	5
03D - Eye Lotion	CERAMIDE AP	1
12C - Face and Neck (exc shave)	CERAMIDE AP	11
12F - Moisturizing	CERAMIDE AP	1

12G - Night	CERAMIDE AP	1
03D - Eye Lotion	CERAMIDE EOP	1
12C - Face and Neck (exc shave)	CERAMIDE EOP	11
12F - Moisturizing	CERAMIDE EOP	1
12G - Night	CERAMIDE EOP	1
03D - Eye Lotion	CERAMIDE EOS	1
12C - Face and Neck (exc shave)	CERAMIDE EOS	11
12F - Moisturizing	CERAMIDE EOS	1
12G - Night	CERAMIDE EOS	1
01C - Other Baby Products	CERAMIDE NP	1
03D - Eye Lotion	CERAMIDE NP	2
12C - Face and Neck (exc shave)	CERAMIDE NP	11
12F - Moisturizing	CERAMIDE NP	1
12G - Night	CERAMIDE NP	1
03D - Eye Lotion	CERAMIDE NS	1
12C - Face and Neck (exc shave)	CERAMIDE NS	11
12F - Moisturizing	CERAMIDE NS	1
12G - Night	CERAMIDE NS	1
03D - Eye Lotion	HYDROXYPALMITOYL SPHINGANINE	3
03G - Other Eye Makeup Preparations	HYDROXYPALMITOYL SPHINGANINE	2
07C - Foundations	HYDROXYPALMITOYL SPHINGANINE	2
07E - Lipstick	HYDROXYPALMITOYL SPHINGANINE	10
07I - Other Makeup Preparations	HYDROXYPALMITOYL SPHINGANINE	1
11A - Aftershave Lotion	HYDROXYPALMITOYL SPHINGANINE	1
11E - Shaving Cream	HYDROXYPALMITOYL SPHINGANINE	1
12A - Cleansing	HYDROXYPALMITOYL SPHINGANINE	3
12C - Face and Neck (exc shave)	HYDROXYPALMITOYL SPHINGANINE	9
12D - Body and Hand (exc shave)	HYDROXYPALMITOYL SPHINGANINE	1
12F - Moisturizing	HYDROXYPALMITOYL SPHINGANINE	18
12G - Night	HYDROXYPALMITOYL SPHINGANINE	1
12J - Other Skin Care Preps	HYDROXYPALMITOYL SPHINGANINE	5
03F - Mascara	2-OLEAMIDO-1,3-OCTADECANEDIOL	43
03G - Other Eye Makeup Preparations	2-OLEAMIDO-1,3-OCTADECANEDIOL	3
05A - Hair Conditioner	2-OLEAMIDO-1,3-OCTADECANEDIOL	64
05B - Hair Spray (aerosol fixatives)	2-OLEAMIDO-1,3-OCTADECANEDIOL	2
05F - Shampoos (non-coloring)	2-OLEAMIDO-1,3-OCTADECANEDIOL	39
05G - Tonics, Dressings, and Other Hair Grooming Aids	2-OLEAMIDO-1,3-OCTADECANEDIOL	18
05I - Other Hair Preparations	2-OLEAMIDO-1,3-OCTADECANEDIOL	127
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	2-OLEAMIDO-1,3-OCTADECANEDIOL	2
06D - Hair Shampoos (coloring)	2-OLEAMIDO-1,3-OCTADECANEDIOL	1

06H - Other Hair Coloring Preparation	2-OLEAMIDO-1,3-OCTADECANEDIOL	3
07C - Foundations	2-OLEAMIDO-1,3-OCTADECANEDIOL	1
07E - Lipstick	2-OLEAMIDO-1,3-OCTADECANEDIOL	2
07F - Makeup Bases	2-OLEAMIDO-1,3-OCTADECANEDIOL	1
07G - Rouges	2-OLEAMIDO-1,3-OCTADECANEDIOL	1
07I - Other Makeup Preparations	2-OLEAMIDO-1,3-OCTADECANEDIOL	1
11A - Aftershave Lotion	2-OLEAMIDO-1,3-OCTADECANEDIOL	1
11E - Shaving Cream	2-OLEAMIDO-1,3-OCTADECANEDIOL	1
12A - Cleansing	2-OLEAMIDO-1,3-OCTADECANEDIOL	1
12C - Face and Neck (exc shave)	2-OLEAMIDO-1,3-OCTADECANEDIOL	5
12D - Body and Hand (exc shave)	2-OLEAMIDO-1,3-OCTADECANEDIOL	2
12F - Moisturizing	2-OLEAMIDO-1,3-OCTADECANEDIOL	24
12G - Night	2-OLEAMIDO-1,3-OCTADECANEDIOL	1
12J - Other Skin Care Preps	2-OLEAMIDO-1,3-OCTADECANEDIOL	9
03D - Eye Lotion	CAPROOYL PHYTOSPHINGOSINE	2
07B - Face Powders	CAPROOYL PHYTOSPHINGOSINE	5
07C - Foundations	CAPROOYL PHYTOSPHINGOSINE	3
12C - Face and Neck (exc shave)	CAPROOYL PHYTOSPHINGOSINE	12
12F - Moisturizing	CAPROOYL PHYTOSPHINGOSINE	1
12G - Night	CAPROOYL PHYTOSPHINGOSINE	1
03D - Eye Lotion	CAPROOYL SPHINGOSINE	1
12C - Face and Neck (exc shave)	CAPROOYL SPHINGOSINE	11
12F - Moisturizing	CAPROOYL SPHINGOSINE	1
12G - Night	CAPROOYL SPHINGOSINE	1

Personal Care Products Council
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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: December 1, 2014

SUBJECT: Comments on the Draft Report Prepared for the December 8-9, 2014 CIR Expert Panel Meeting: Safety Assessment of Ceramides as Used in Cosmetics

Key Issue

Although they may not be commonly used cosmetic ingredients, it is not correct to state that pseudo-ceramides are not cosmetic ingredients. The pseudo-ceramide called SLE-66 has an INCI name, Cetyl-PG Hydroxyethyl Palmitamide (24 uses reported to the VCRP [2013 data]). At the June meeting, the CIR Expert Panel looked at the structure of this pseudo-ceramide and based on the structure determined it was not appropriate to include it in the CIR report on ceramide ingredients.

Additional Comments

Cosmetic Use - Please correct "0 0.7%"

Reproductive and Developmental Toxicity, Summary - Was there more than one 1000 mg/kg/day dose group as the last paragraph and the Summary say "In a 1000 mg/kg/day dose group..."

Genotoxicity, Summary, Table 6 - The genotoxicity study (reference 40) was completed in Chinese hamster lung "cells" not "tissue".

Dermal Irritation, Summary, Table 8 - Hydroxypalmitoyl Sphinganine and 2-Oleamido-1,3 Octadecanediol were tested as provided (as powders) - they were tested undiluted.

Summary - In the Summary, please note that ceramides are normal constituents of skin and that they have a physiological role.

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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 21, 2015

SUBJECT: Comments on the Tentative Report: Safety Assessment of Ceramides as Used in Cosmetics

Key Issues

The report needs to make it clear that the ingredients derived from phytosphingosine are not derived from animal sources.

Chemistry - The description of the ingredients in the Chemistry section is appropriate for the ingredients with "Ceramide" in the name, but some additional information should be added to this section to describe the "ceramide-like" ingredients such as Hydroxypalmitoyl Sphinganine and 2-Oleamido-1,3-Octadecanediol.

Additional Comments

Cosmetic Use - Please delete the word "current" from the first sentence, as the information is unlikely to be current by the time the report is published.

Please revise the following sentence: "Most of the other use concentrations that were reported had similar use concentrations." The following may be an acceptable replacement: "Use concentrations reported for other cosmetic product categories were similar."

Repeated Dose Exposure, Dermal - Non-Human, 1-Oleamido-1,3-Octadecanediol - When available, please include the surface area size to which the test compound was applied. In this case, the investigators shaved a total area of about 40 cm^2 and applied 1-Oleamido-1,3-Octadecanediol to about half of the shaved area.

Discussion - Please state the compound (1-Oleamido-1,3-Octadecanediol) for which a screening reproductive and developmental toxicity study was completed.

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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: January 29, 2015

SUBJECT: Comments on the Tentative Report: Safety Assessment of Ceramides as Used in Cosmetics

The CIR Science and Support Committee appreciates the opportunity to comment on the tentative safety assessment on ceramide ingredients.

The Introduction is misleading in that it suggests that these ingredients may be derived from bovine central nervous system tissue. The CIR report needs to make it clear that because of concerns about potential transmission of bovine spongiform encephalopathy (BSE), cosmetic products are not permitted to contain ingredients made from bovine specified risk materials which includes the central nervous system (see attached 21CFR700.27). In addition, ingredients made from specified risk materials are not permitted for use in cosmetics in many other countries including Europe (see European Cosmetic Regulations Annex II, entry 419) and Canada (see Canada's Cosmetic Ingredient Hotlist).

The report should also make it clear that by definition some of these ingredients (Ceramide 1 [retired], Ceramide 1 A [retired], Ceramide EOP, Ceramide 3 [retired], Ceramide NP, Ceramide 6 II [retired], Ceramide AP, Hydroxylauroyl Phytosphingosine, Hydroxycaproyl Phytosphingosine, Hydroxycapryloyl Phytosphingosine, Caprooyl Phytosphinogsine) are derived from plants. These ingredients either have phytosphingosine in the INCI name or definition. In the new naming system, phytosphingosine is represented by P in the name. It is only those ingredients derived from sphingosine (S in the name using the new naming system) or sphinganine (G in the new naming system) (Ceramide 2 [retired], Ceramide NS, Ceramide NG, Ceramide 4 [retired], Ceramide 5 [retired], Ceramide AS, Ceramide EOS, Ceramide NS Dilaurate, Caproyl Sphingosine, Caprooyl Sphingosine) that could possibly be derived from animals

In the Discussion, the CIR Expert Panel should deal with the issue of potential bovine nervous system-derivation of some ceramide ingredients by clearly stating that ingredients derived from bovine specified risk materials are not permitted for use in cosmetics.

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not include the requirement in paragraph (b) of this section that the indicator or barrier to entry be distinctive by design. Products packaged for retail sale after May 5, 1983, as required to be in compliance with all aspects of the regulations without regard to the retail level effective date.

[47 FR 50451, Nov. 5, 1982; 48 FR 1707, Jan. 14, 1983; 48 FR 11427, Mar. 18, 1983, as amended at 48 FR 16664, Apr. 19, 1983; 48 FR 37624, Aug. 19, 1983]

EFFECTIVE DATE NOTE: See 48 FR 41579, Sept. 16, 1983, for a document announcing an interim stay of the effective date of certain provisions in paragraph (e)(3) of § 700.25.

§ 700.27 Use of prohibited cattle materials in cosmetic products.

(a) *Definitions.* The definitions and interpretations of terms contained in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) apply to such terms when used in this part. The following definitions also apply:

(1) Prohibited cattle materials means specified risk materials, small intestine of all cattle except as provided in paragraph (b)(2) of this section, material from nonambulatory disabled cattle, material from cattle not inspected and passed, or mechanically separated (MS) (Beef). Prohibited cattle materials do not include the following:

(i) Tallow that contains no more than 0.15 percent insoluble impurities, tallow derivatives, hides and hide-derived products, and milk and milk products, and

(ii) Cattle materials inspected and passed from a country designated under paragraph (e) of this section.

(2) *Inspected and passed* means that the product has been inspected and passed for human consumption by the appropriate regulatory authority, and at the time it was inspected and passed, it was found to be not adulterated.

(3) *Mechanically Separated (MS)(Beef)* means a meat food product that is finely comminuted, resulting from the mechanical separation and removal of most of the bone from attached skeletal muscle of cattle carcasses and parts of carcasses that meet the specifications contained in 9 CFR 319.5, the regulation that prescribes the standard of identity for MS (Species).

(4) *Nonambulatory disabled cattle* means cattle that cannot rise from a recumbent position or that cannot walk, including, but not limited to, those with broken appendages, severed tendons or ligaments, nerve paralysis, fractured vertebral column, or metabolic conditions.

(5) *Specified risk material* means the brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia of cattle 30 months and older and the tonsils and distal ileum of the small intestine of all cattle.

(6) *Tallow* means the rendered fat of cattle obtained by pressing or by applying any other extraction process to tissues derived directly from discrete adipose tissue masses or to other carcass parts and tissues. Tallow must be produced from tissues that are not prohibited cattle materials or must contain not more than 0.15 percent insoluble impurities as determined by the method entitled "Insoluble Impurities" (AOCS Official Method Ca 3a-46), American Oil Chemists' Society (AOCS), 5th Edition, 1997, incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51, or another method equivalent in accuracy, precision, and sensitivity to AOCS Official Method Ca 3a-46. You may obtain copies of the method from the AOCS (*http://www.aocs.org*) 2211 W. Bradley Ave. Champaign, IL 61821. Copies may be examined at the Center for Food Safety and Applied Nutrition's Library, 5100 Paint Branch Pkwy., College Park, MD 20740, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*

(7) *Tallow derivative* means any chemical obtained through initial hydrolysis, saponification, or transesterification of tallow; chemical conversion of material obtained by hydrolysis, saponification, or transesterification may be applied to obtain the desired product.

(b) *Requirements.* (1) No cosmetic shall be manufactured from, processed with, or otherwise contain, prohibited cattle materials.

(2) The small intestine is not considered prohibited cattle material if the distal ileum is removed by a procedure that removes at least 80 inches of the uncoiled and trimmed small intestine, as measured from the caeco-colic junction and progressing proximally towards the jejunum, or by a procedure that the establishment can demonstrate is equally effective in ensuring complete removal of the distal ileum.

(c) *Records.* (1) Manufacturers and processors of a cosmetic that is manufactured from, processed with, or otherwise contains, material from cattle must establish and maintain records sufficient to demonstrate that the cosmetic is not manufactured from, processed with, or does not otherwise contain, prohibited cattle materials.

(2) Records must be retained for 2 years after the date they were created.

(3) Records must be retained at the manufacturing or processing establishment or at a reasonably accessible location.

(4) The maintenance of electronic records is acceptable. Electronic records are considered to be reasonably accessible if they are accessible from an onsite location.

(5) Records required by this section and existing records relevant to compliance with this section must be available to FDA for inspection and copying.

(6) When filing entry with U.S. Customs and Border Protection, the importer of record of a cosmetic manufactured from, processed with, or otherwise containing, cattle material must affirm that the cosmetic was manufactured from, processed with, or otherwise contains, cattle material and must affirm that the cosmetic was manufactured in accordance with this section. If a cosmetic is manufactured from, processed with, or otherwise contains, cattle material, then the importer of record must, if requested, provide within 5 days records sufficient to demonstrate that the cosmetic is not manufactured from, processed with, or does not otherwise contain, prohibited cattle material.

(7) Records established or maintained to satisfy the requirements of this subpart that meet the definition of electronic records in §11.3(b)(6) of this chapter are exempt from the requirements of part 11 of this chapter. Records that satisfy the requirements of this subpart but that are also required under other applicable statutory provisions or regulations remain subject to part 11 of this chapter.

(d) *Adulteration.* Failure of a manufacturer or processor to operate in compliance with the requirements of paragraph (b) or (c) of this section renders a cosmetic adulterated under section 601(c) of the act.

(e) *Process for designating countries.* A country seeking designation must send a written request to the Director, Office of the Center Director, Center for Food Safety and Applied Nutrition, Food and Drug Administration, at the address designated in 21 CFR 5.1100. The request shall include information about a country's bovine spongiform encephalopathy (BSE) case history, risk factors, measures to prevent the introduction and transmission of BSE, and any other information relevant to determining whether specified risk materials, the small intestine of cattle except as provided in paragraph (b)(2) of this section, material from non-ambulatory disabled cattle, or MS (Beef) from cattle from the country should be considered prohibited cattle materials. FDA shall respond in writing to any such request and may impose conditions in granting any such request. A country designation granted by FDA under this paragraph will be subject to future review by FDA, and may be revoked if FDA determines that it is no longer appropriate.

[70 FR 53068, Sept. 7, 2005, as amended at 71 FR 59668, Oct. 11, 2006; 73 FR 20794, Apr. 17, 2008]

§ 700.35 Cosmetics containing sunscreen ingredients.

(a) A product that includes the term "sunscreen" in its labeling or in any other way represents or suggests that it is intended to prevent, cure, treat, or mitigate disease or to affect a structure or function of the body comes