
Safety Assessment of Alkyl Betaines

as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: February 21, 2014
Panel Meeting Date: March 17-18, 2014

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, 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, DPA. This safety assessment was prepared by Christina L. Burnett, Scientific Analyst/Writer, and Bart Heldreth, Ph.D., Chemist CIR.



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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett
Scientific Writer/Analyst
Date: February 21, 2014
Subject: Draft Final Report on Alkyl Betaines

At the December 2013 meeting, the Panel issued a tentative safety assessment on alkyl betaines with the conclusion that the 11 ingredients listed in the report are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

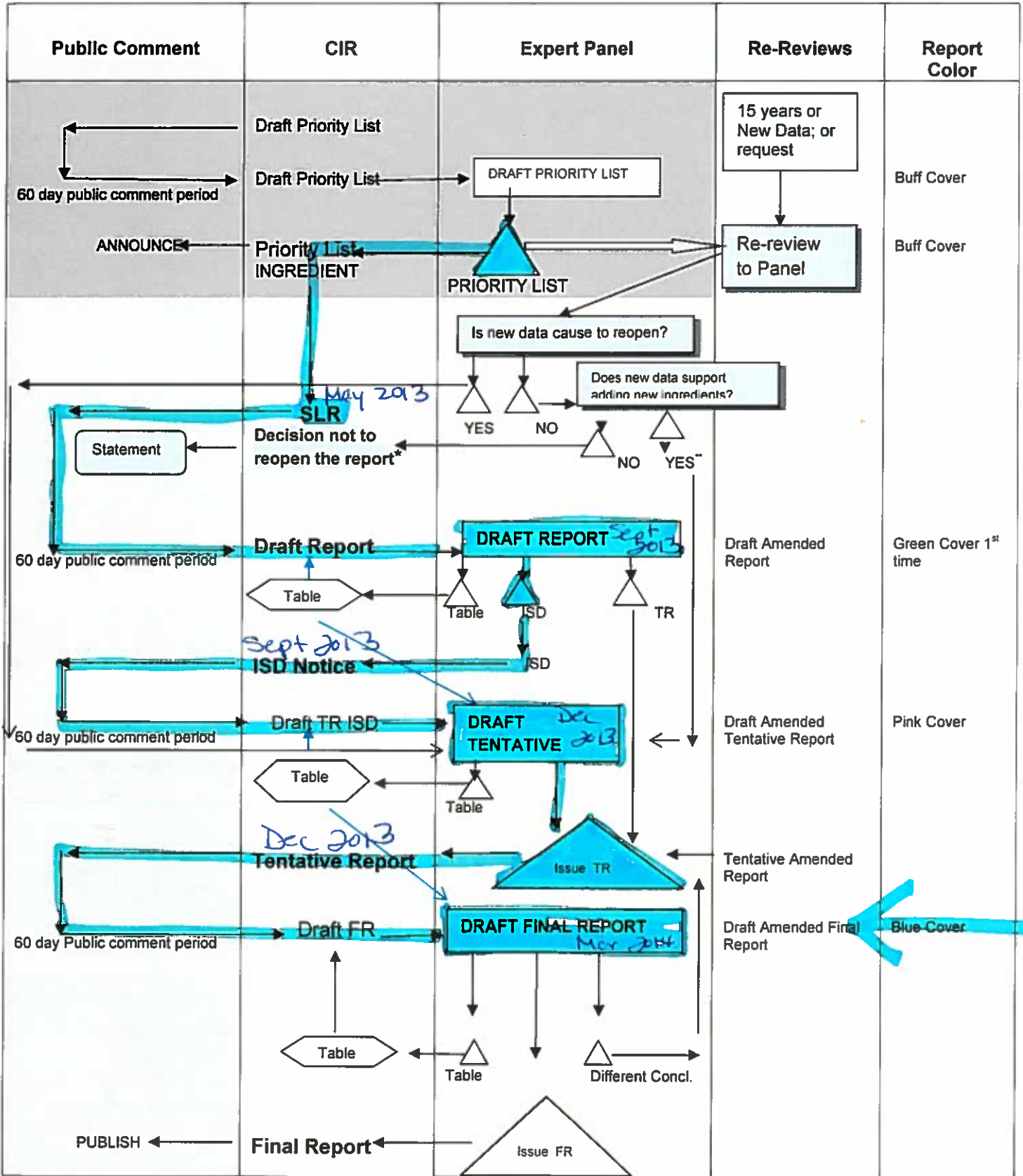
Since December, no new data have been received. Comments that were received from the Council prior to the December meeting, as well as those on the tentative safety assessment, have been considered. The comments are available for your review in this report package.

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

Allyl Betaines

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SAFETY ASSESSMENT FLOW CHART

Mar 2014



Alkyl Betaines History

May 2013 – Scientific Literature Review announced.

September 2013 - The Panel requested additional data to support the safety of 11 alkyl betaines. The additional data needed were (1) method of manufacturing, and (2) impurities. CIR received legal permission to summarize data on the European Chemical Agency's (ECHA's) website. The Panel reviewed a table with data on a C12-C14 betaine analog.

December 2013 – The Panel received method of manufacturing and impurities data from a supplier of coco-betaine. This data along with basic composition data on a betaine analog from ECHA's database and basic method of manufacturing data on food-grade betaine fulfilled the insufficient data needs. The Panel issued a tentative safety assessment on alkyl betaines with the conclusion that these ingredients are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

Alkyl Betaines Data Profile – March 2014 – Writer, Christina Burnett

	In-Use	Composition /Impurities	Method of Mfg	Toxicokinetics	Acute Tox - Derm	Acute Tox - Oral	Acute Tox - Inhalation	Acute Tox - IV	Acute Tox - Other	Repeated Dose - Dermal	Repeated Dose - Oral	Repeated Dose - Inhalation	Repeated Dose -IV	Repeated Dose - Other	Repro/Dev Tox	Genotoxicity	Carcinogenicity/Tumor Promoton	Dermal Irritation – Non-Human	Dermal Irritation-Human	Dermal Sens – Non-Human	Dermal Sens – Human	Ocular /Mucosal Irritation	Case Studies	Phototoxicity/Photosensitization
Betaine	X	X	X	X		X		X			X					X	X		X	X	X	X		
Behenyl Betaine	X																							
Cetyl Betaine	X			X	X	X			X		X				X									
Coco-Betaine	X	X	X			X					X							X	X	X		X	X	
Decyl Betaine																								
Hydrogenated Tallow Betaine																								
Lauryl Betaine	X			X	X	X			X										X		X	X		
Myristyl Betaine	X																							
Oleyl Betaine	X																							
Stearyl Betaine	X																							
Tallow Betaine																								
Betaine analog C12-C14		X				X					X				X	X		X		X		X		

“X” indicates that data were available in the category for that ingredient.

Search Strategy for Alkyl Betaines

January 2013: SCIFINDER, TOXLINE, and PUBMED search for Alkyl Betaines using INCI name and CAS #

Searches were then further filtered for adverse effects and document type.

Further limits were placed on betaine to remove efficacy studies, and on coco-betaine, to remove CAPB relation.

	TOXLINE, minus PUBMED	SCIFINDER	PUBMED
Betaine	6 (under lauryl)	5953	2468
Behenyl Betaine	0	3	1
Cetyl Betaine	6	66	0
Coco-Betaine	3	0	1
Decyl Betaine	0	21	0
Hydrogenated Tallow Betaine	0	0	0
Lauryl Betaine	2	201	1
Myristyl Betaine	0	58	0
Oleyl Betaine	1	6	0
Stearyl Betaine	0	27	0
Tallow Betaine	0	0	0

Total references ordered: 14

Search Updated October 18, 2013 and January 24, 2014

December 9, 2013 CIR Expert Panel Meeting

Marks' Team

DR. MARKS: Again, for the record, Ron Shank, he will not be making the meeting. He will be sending his flash drive with comments.

Okay. The next ingredient or ingredients are the alkyl betaines. At the September 2013 meeting, the expert panel issued an insufficient data announcement where method of manufacturing and impurities. And I thought that was met, and so did Ron Shank. So I think we've met the insufficient data, and that we could move forward issuing a tentative report on the alkyl betaines with a "safe when formulated to be non-irritating." And I will be presenting that at the combined meeting.

Comments, Christina or Wilma? And then let me go back and let me -- Tom. Tom, can you hear me? Apparently not. He's not speaking to American Airlines anymore. And you had mentioned to Carla that -- Tom is up, so if we could get Tom on the phone, that would be good.

DR. BERGFELD: This is one that I had made a note to myself that the references for the studies were in the table. But I wanted to go back and re-check whether I had seen them in the text, because I think I did not. That's why I was --

MS. BURNETT: No. I had summarized --

DR. BERGFELD: Yeah, you summarized -- no, it doesn't matter to me, but not all the documents do it that way.

MS. BURNETT: Right. Right. Well, we'll work together to make sure that we're consistent.

DR. BERGFELD: Whatever you do, yeah. Okay. No. No, I just wondered, I was going back. Do you say see table or anything?

MS. BURNETT: Yes.

DR. BERGFELD: Okay. That's fine. That would be fine with me. But then when I went to other documents, they're in both places, and then --

MS. BURNETT: The Council made some comments.

DR. BERGFELD: Okay.

MS. BURNETT: And I think when we just briefly discussed some of them, I think it depends on how much data we were summarizing. If it was a lengthy thing, people kind of put the references in. If it's a short thing, then we tend to just let the table speak for itself. But we'll make sure that we're all doing it consistently so that it's --

DR. BERGFELD: Yeah, that would be nice.

MS. BURNETT: It's really easy just to insert --

DR. BERGFELD: All right.

DR. ANSELL: We also have a comment concerning the referencing of the REACH. We think it's great that the ECHA date is being included, but we should be clear that ECHA itself is not an author. These are being authored by consortia.

MS. BURNETT: Right. We're at odds with the Legal Department then because the Legal Department told us that it was perfectly appropriate to reference ECHA because Joe Q. Public --

DR. ANSELL: No, no, no. We agreed to the referencing. We don't think we should call them the author of the reports.

MS. BURNETT: Oh, I see that.

DR. ANSELL: ECHA is the source of the reports. They don't actually author anything.

MS. BURNETT: Is it in the text or in the reference section?

DR. ANSELL: They should not be listed as the author in the references section.

DR. BERGFELD: How would you list them?

DR. ANSELL: Source.

DR. BERGFELD: Source?

MS. BURNETT: We're going to have to manually put in "source" because how the reference program puts it you have to put in author, whether it's an actual entity or not. So we'll figure out how to do that. It's just for public. You know, when we're referencing website, they're going to see that they're going to be ECHA --

DR. ANSELL: Right. No, we think that all that's fine.

MS. BURNETT: Okay.

DR. ANSELL: You will note that Carol (inaudible) every single time.

MS. BURNETT: Yes.

DR. BERGFELD: Could I also make a comment? This is one that some of the documentation was scanned sideways.

DR. MARKS: Thanks, Wilma.

DR. ANSELL: Which is terrible on the iPad because when you turn the iPad sideways --

DR. MARKS: It turns, too.

DR. BERGFELD: Can you turn this on the computer?

MS. BURNETT: Which PDF page, please?

DR. BERGFELD: Well, it's right above the comments.

DR. ANSELL: Somewhere in view it should say.

DR. BERGFELD: View?

DR. ANSELL: Yes, ma'am.

DR. BERGFELD: Rotate view?

DR. ANSELL: Right, rotate --

MS. BURNETT: Everything is showing up --

DR. MARKS: You can see at what level of sophistication we are in using this.

DR. BERGFELD: Oh, my god. Yeah.

DR. MARKS: Yeah.

DR. BERGFELD: Thank you.

DR. MARKS: Okay.

DR. BERGFELD: Not all of them are that way, so --

DR. MARKS: So to save us from having to manually go in and rotate, let's see if we can't --

Any other comments? If not, then I will move tomorrow we move forward with a tentative report on the alkyl betaines with the conclusion of "safe when formulated to be non-irritating."

Okay. Any other comments?

(No response.)

Belsito's Team

DR. BELSITO: Okay, great. Okay, alkyl betanes' or be' tanes (phonetic)?

How did we decide this should be pronounced? Betaines.

MS. BURNETT: Derived from beets originally, so Beet-a-ene.

DR. BELSITO: So, at the September meeting, Christina not only taught us how to pronounce these. We determined that the data submitted were insufficient to support the safety of 11 alkyl betaines and requested additional data on manufacturing impurities. We got data on manufacturing and impurities for coco betaine. Basic composition data on betaine analogs from the ECCA database that we originally weren't clear that we could use legally, but now I've gotten a legal go ahead. We've got some manufacturing on food grade betaines and technical comments from the Council, and with all of that that we have received the question what are we doing with this document? And again I said safe as used when formulated to be nonirritating and had only a couple minor edits.

DR. LIEBLER: I agree.

DR. SNYDER: I agree. I just had one query about the tallow. Does that mean it comes from tallow? Is that a source, animal source then?

DR. BELSITO: Where was that, Paul?

DR. SNYDER: There's tallow betaine.

DR. BELSITO: Hydrogenated tallow betaine and tallow betaine.

DR. SNYDER: Yes.

DR. BRESLAWEC: Yeah, I think

DR. BELSITO: We have no use for tallow betaine and no use for hydrogenated tallow betaine.

DR. BRESLAWEC: I think CIR has a boilerplate that they can use when referring to tallow derived ingredients.

DR. BELSITO: Okay.

DR. BRESLAWEC: Thought I had incorporated it, but perhaps I didn't.

DR. BELSITO: No, I just scanned the document. You don't get to "tallow" until you well, maybe, let me go further. I didn't finish it.

(Pause)

DR. BELSITO: No, it wasn't included.

DR. BRESLAWEC: Oh, it is.

DR. EISENMANN: Yes, it is. In the discussion the panel expressed concern about the dangers inherent in using animal derived ingredients, namely and I was wondering if you should say "such as" and give an example, namely, the transmission of infectious agents. They stress that these ingredients "must be free of detectable pathogens, viruses, or infectious agents, e.g., BSE. The ingredients should be produced according to good manufacturing procedures and should conform to regulations for producing substances from animal derived materials." So, it is in the discussion.

DR. BELSITO: Where are you?

DR. EISENMANN: It just doesn't say "tallow." I'm in the discussion.

DR. BELSITO: What page? Because I'm not seeing it.

DR. EISENMANN: I don't have a PDF. It's in the discussion. It's the paragraph under the link to the CIR findings under the inhalation paragraph.

DR. BELSITO: I don't have that.

DR. KLAASSEN: I don't think we have that.

MS. BURNETT: Weird. I don't have it on my

DR. EISENMANN: Amino acid amino alloys, right? Is that the report?

DR. BELSITO: No, no, no, no.

MS. BURNETT: Betaines.

DR. EISENMANN: Betaine, okay. Well, that's the paragraph that should go in.

MS. BURNETT: Okay.

DR. EISENMANN: So, I found it in the

MS. BURNETT: That's why I remember seeing it in

DR. EISENMANN: I remember it too, so then, but that's the paragraph.

DR. SNYDER: So, place the BSE into the

DR. BELSITO: So, at that point, at the end of when we talk about the inhalation, then we'll add the paragraph from which report, Carol?

DR. EISENMANN: The one we were just doing, alkyl amides.

MS. BURNETT: Okay, now I see it.

DR. BELSITO: Okay, anything else?

(No response)

DR. BELSITO: Okay.

DR. LIEBLER: Curt, one minor question.

DR. BELSITO: Sure.

DR. LIEBLER: On page 22, the very top, there's 8.7 percent. Is that this was one of these, was it the (inaudible). Was that 8.7 absolute concentration or 8.7 percent based on a 30 percent solution, Christina?

MS. BURNETT: I'm sorry, what page were you on again?

DR. BELSITO: Page 22, second line.

MS. BURNETT: And could you restate the question? I'm sorry.

DR. LIEBLER: 8.7 percent, is that the absolute concentration? Or is that 8.7 percent of the 30 percent solution?

MS. BURNETT: I don't remember.

DR. BELSITO: The alkyl betaines are not provided pure. They're provided from the manufacturers of 30 percent solution. That's what you're alluding to, Dan, correct?

DR. LIEBLER: That's right, yeah. I just want to make sure that that's correct.

DR. BELSITO: And so is it 8 percent of alkyl betaines, or is it 8 percent of what was provided by the manufacturer?

DR. EISENMANN: When I asked for concentration of use, I asked for the actual ingredient. They're actually telling me I would have to back again to the company that said that. They told me 8.7 percent, so I would make the assumption that it's of the ingredient. That's what they're supposed to tell me. But if you think it's unusually high or something, then, I mean, it's a rinse off I believe. It's the hair dyes, isn't it?

DR. LIEBLER: No, I don't have any basis to think it's either high or low. I just wanted to check that it was asked for as the absolute concentration, and you just answered that, so I'm fine with it then.

DR. EISENMANN: Okay. I mean, that's what I asked for. I can't necessarily guarantee that's what they're telling me.

DR. LIEBLER: Yeah. No, that's enough. That's fine.

DR. BELSITO: Okay, anything else? Okay. So, then, next

Full Panel

DR. BERGFELD: Dr. Marks, you're up, alkyl betaines.

DR. MARKS: So in September the panel came to the conclusion with insufficient data announcement. We wanted to know method of manufacturing and impurities. Our team felt -- and Ron Hill, you can chime in--Ron Shank and Tom felt we now are okay with that and that we could move forward issuing a tentative report on the alkyl betaines safe formulated to be non-irritating.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion?

DR. BELSITO: Yes.

DR. BERGFELD: Yes. Don?

DR. BELSITO: Tallow is one of the ones that are listed, so we need to take the paragraph from the alkyl amides regarding animal derived ingredients, specifically tallow, and insert it into the discussion on this document.

DR. BERGFELD: Any other additions? Ron Hill?

DR. HILL: Yeah, what I was really looking for on the coco betaine was actually the fatty acid composition, which I'm not sure --we don't need necessarily to get that from industry because we--I mean, I assume it's consistent with what we normally see with coconut oil derived ingredients. But for the CIR staff member who worked on this, that's what I was looking for because that allows for the read across. And what's in there is not bad at all.

DR. BERGFELD: So you propose?

DR. HILL: I'm just proposing, and that's editorial, I guess, that that information get captured. What are the typical ranges?

DR. BERGFELD: Okay.

DR. HILL: So that the read across gets properly developed here because it's not right now.

MS. BURNETT: Are you looking at Figure 2, Table 1?

DR. HILL: Okay, you got--

MS. BURNETT: Where the definitions and structures are.

DR. HILL: Give me a table number or a PDF page number.

MS. BURNETT: It's Figure 2. I'm sorry, I don't have a PDF of it.

DR. HILL: Okay, hang on.

DR. HELDRETH: PDF page 27.

DR. HILL: Thank you. Okay. No, I didn't note that that was there now.

Okay. So yes, that together with the cetyl, and then the only other thing I flagged since I wasn't here this morning is there's some developmental toxicity that shows up I think at a lot higher concentrations for the cetyl. My question

was do we know enough about the leave on usages of this and have we calculated what the maximum possible exposure is likely to be or are we just going by the stuff is fairly hydrophobic and we're not worried about penetrability?

DR. BERGFELD: I can't answer that. Dan Liebler, did you hear Ron Hill's statement?

DR. LIEBLER: Yeah, I heard it. I guess I'm not sure I have a concern there.

DR. HILL: If he doesn't and nobody else does, then I don't either.

DR. BERGFELD: Okay. Well, we'll make note that it's in the minutes and if it needs to be reexamined, we will do that in the future.

DR. HILL: Thank you.

DR. BERGFELD: All right, then I will call the question if there are not further comments. All those in favor? Unanimous.

DR. LIEBLER: Aye.

DR. BERGFELD: Aye coming from the phone here. I heard Dan. Is Tom there?

DR. SLAGA: Yes. Tom, yes.

DR. BERGFELD: Yes, okay. All right. Thank you very much.

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ABSTRACT

The Cosmetic Ingredient Review Expert Panel reviewed the product use, formulation and safety data of eleven alkyl betaines, which mostly function as hair and skin-conditioning agents. With the exception of betaine, alkyl betaines may also function as antistatic agents, surfactants-cleansing agents, and viscosity increasing agents in cosmetic products. Although there are data gaps, the shared chemical core structure, similar functions and concentrations in cosmetics, and the expected similarities in physicochemical properties, enabled grouping these ingredients and reading across the available toxicological data to support the safety assessment of each individual compound in the entire group. The Panel concluded alkyl betaines were safe as cosmetic ingredients in the present practices of use and concentration, when formulated to be non-irritating.

INTRODUCTION

This safety assessment addresses the safety of 11 alkyl betaines as used in cosmetics. The parent compound, betaine, is a naturally occurring *N*-trimethylated amino acid, also called trimethylglycine, and can be isolated from sugar beets.¹ It is a common component in the human diet. These cosmetic ingredients mainly function as hair and skin-conditioning agents.² With the exception of betaine, alkyl betaines may also function as antistatic agents, surfactants-cleansing agents, and viscosity increasing agents. CIR has reviewed the safety of cocamidopropyl betaine and related amidopropyl betaines as used in cosmetics.³

The common core chemical structure, similar functions and concentrations in cosmetics, and the predicted physicochemical properties enabled grouping these ingredients and reading across the available toxicological data to support the safety assessment of each individual compound in the entire group.

Toxicological data on betaine and betaine analogs (synonym: betaines, C12-14 (even numbered)-alkyldimethyl or C12-C14 alkyldimethyl betaines) in this safety assessment were obtained from robust summaries of data submitted to the European Chemical Agency (ECHA) by private companies as part of the REACH chemical registration process. These data are available on the ECHA website.^{4,5}

CHEMISTRY

The definitions of the 11 alkyl betaines in this safety assessment can be found in Table 1, and formulas and idealized structures of these ingredients can be found in Figure 2.

The alkyl betaines are zwitterionic ingredients comprised of tertiary ammonium substituted acetate. These ingredients have a core structure of 2-(alkyldimethylammonio)acetate (i.e., *N,N,N*-trisubstituted glycine) (Figure 1).

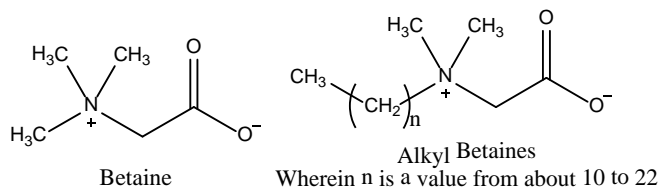


Figure 1. Betaine and the Alkyl Betaines

Therein, the “alkyl” is either methyl, as in the case of betaine itself, or a longer chain alkyl group ranging in length from about ten (e.g., decyl betaine) to about twenty-two (e.g., behenyl betaine) carbons. Ten to twenty-two carbons are an estimate, however, as the compositions of the ingredients derived from plant and animal sources (e.g., coco-betaine, tallow betaine, and hydrogenated tallow betaine) are variable.

The zwitterionic structures of these ingredients make them amphoteric, a hallmark characteristic of classical surfactants. The fatty chains, found on most of these ingredients, add a lipophilic tail to these hydrophilic head groups, further imparting surfactant properties. Those ingredients for which chemical property data were available are colorless, crystalline materials with good solubility in water and polar organic solvents. While ingredients that only vary from these by incremental alkyl chain length changes are likely to have similar profiles, chemical and physical properties were neither publicly available, nor submitted by other parties, for any of the other ingredients.

Physical and Chemical Properties

Available chemical properties can be found in Table 2.

Method of Manufacturing

Betaine

Betaine (food-grade) may be extracted from sugar beets via liquid chromatography separation from sugar beet molasses.^{6,7} It is subsequently refined and crystallized. Betaine anhydrous (as animal feed additive) is produced by reacting chloroacetic acid and sodium hydroxide with heat and stirring.⁸ Trimethylamine is then added to the mixture and the resultant solutions filtered and purified. Betaine hydrochloride (as animal feed additive) follows the same synthesis pathway as betaine anhydrous except hydrochloric acid is added and the filtrate is purified.⁸

Coco-betaine

In data supplied by a manufacturer, coco-betaine is produced by reacting fatty dimethyl amines from coconuts with chloroacetic acid in aqueous solution.⁹

Impurities

Betaine

Betaine (food-grade) contains very small quantities of chloride, sulfate, and heavy metals.⁷ Trace analysis show very small amounts of PCB, PAH and dioxins. No pesticide traces have been detected. Betaine does not contain methanol, ethanol, or isopropanol (limits of detections were 5.0, 2.5, and 0.5 ppm, respectively).

Betaine anhydrous and betaine hydrochloride (as animal feed additives) contained < 2.0 mg/kg arsenic and < 10 mg/kg heavy metals (expressed as lead).⁸ Dioxin content was < 0.50 ng/kg and PCB content was < 0.35 mg/kg. Betaine content for the anhydrous and hydrochloride forms was $\geq 96\%$ and $\geq 93\%$, respectively.

Coco-betaine

According to information supplied by a manufacturer, coco-betaine is composed of approximately 31% coco-betaine, 7% sodium chloride, and 62% water.⁹ There are no solvents, preservatives and other additives. The product may contain a maximum of: 100 ppm dichloroacetic acid, 100 ppm monochloroacetic acid, 0.5% free amines, 2% glycolic acid, 20 ppm heavy metals (copper, lead, tin, platinum, palladium, mercury, arsenic, cadmium, antimony, nickel, chromium, and cobalt), 2 ppm arsenic, 10 ppm iron, and < 3% volatile organic compounds.

C12-C14 Alkyldimethyl Betaines

According to information supplied to ECHA, betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine) is comprised of betaine, C12-alkyldimethyl; betaine, C14-alkyldimethyl; (carboxylatomethyl) hexadecyldimethylammonium; sodium chloride; sodium glycolate; and unknown impurities.⁵ Percent composition was not provided and there are no further details.

USE

Cosmetic

Table 3 presents the current product-formulation data for alkyl betaines. Betaine mainly functions as a hair conditioning agent, humectant, and skin-conditioning agent-humectant in cosmetic products.² The remaining alkyl betaines additionally function as antistatic agents, skin-conditioning agents-misc., surfactants-cleansing agents and foam boosters, and viscosity increasing agents. According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), betaine has the most reported uses in cosmetic and personal care products, with a total of 459; the majority of the uses are in leave-on skin care preparations.¹⁰ Lauryl betaine has the second greatest number of overall uses reported, with a total of 338; the majority of those uses are in rinse-off personal cleanliness products. The 8 ingredients with reported VCRP uses are:

- betaine
- behenyl betaine
- cetyl betaine
- coco-betaine
- lauryl betaine
- myristyl betaine
- oleyl betaine and
- stearyl betaine

Three ingredients are included in this safety assessment for which no uses have been reported to the VCRP:

- decyl betaine
- hydrogenated tallow betaine
- tallow betaine

In the Personal Care Products Council's use concentration survey, betaine had a maximum use concentration range of 0.0001% to 8.7%, with the 8.7% reported in rinse-off non-coloring hair conditioners.¹¹ Lauryl betaine had a maximum use concentration range of 0.015% to 8.8%, with 8.8% reported in rinse-off non-coloring hair shampoos. The Council reports that they do not have any suppliers listed for decyl betaine, hydrogenated tallow betaine, stearyl betaine, or tallow betaine.¹²

Betaine and lauryl betaine were reported to be used in hair sprays, body and hand products, non-coloring hair powders, and indoor tanning preparations that may be aerosolized or become airborne and could possibly be inhaled. 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.¹³⁻¹⁶ 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.^{14,15}

Alkyl betaines are not restricted from use in any way under the rules governing cosmetic products in the European Union.¹⁷

Non Cosmetic

A biocide that contains cetyl betaine is currently being studied as a preventative treatment of human immunodeficiency virus type 1 (HIV-1) and other sexually transmitted diseases in vaginal microbicides and contraceptives.^{18,19}

Betaine hydrochloride has been approved by the FDA to treat homocystinuria (by reducing homocysteine levels).²⁰ It is also present as an active ingredient in over-the-counter digestive aids; however, FDA has determined that there are inadequate data to establish general recognition of the safety and effectiveness of the ingredient for this specified use (21 CFR §310.545).

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Betaine

Low percutaneous permeation capability for betaine was observed in a percutaneous absorption study using Franz chambers with freshly isolated human epidermis.⁴ The study followed OECD Guideline 428, but was not GLP compliant. Betaine at 5% in saline or emulsion was applied to the epidermis samples. The exposure was observed for 24 h. Approximately 0.1% of the applied dose in both vehicle types permeated through the epidermis samples.

The pharmacokinetics and acute effects on plasma total homocysteine (tHcy) of orally administered betaine (see use of betaine hydrochloride in treating homocystinuria above) was assessed in healthy human volunteers (3 men and 7 women).²¹ Information on the absorption and elimination of betaine was also developed. In a double-blind crossover study, each subject ingested the betaine in doses of 1, 3, and 6 g mixed with 150 ml orange juice. The doses were ingested 7 days apart following a 12-h overnight fast. Blood samples for serum betaine concentration measurement were drawn just before receiving the betaine dose, at 20-min intervals during the first 3 h, and then at 4-, 7-, and 24-h post dosing. Urine samples were collected before dosing and during the 24-h follow-up period. Within 2 h, a dose-dependent increase on serum betaine concentration was observed. Absorption and elimination of betaine were dose dependent, with urinary excretion of betaine increasing with betaine dose. Only a very small proportion of the ingested betaine was excreted in urine, however, with 3.2%, 4.3%, and 7.4% of the 1, 3, and 6 g doses accounted for, respectively.

Cetyl Betaine and Lauryl Betaine

The absorption of radiolabeled cetyl betaine (5.4 mM) and lauryl betaine (16 mM) was determined using diffusion cells containing excised hairless mouse skin.²² Lauryl betaine was well absorbed into the receptor phase (approximately 50% of the applied dose within 24 h) while cetyl betaine partitioned into the skin but slowed transfer to the receptor phase (approximately 1.3% of the applied dose absorbed within 24 h). Skin digests at the end of the 24 h found that 15% of the applied dose of cetyl betaine and 25% of the applied dose of lauryl betaine were associated with the tissue. This study also examined the effects of cetyl betaine and lauryl betaine (same concentrations as used in the absorption study) on skin barrier function in hairless mouse skin *in vitro*. Excised skin was pretreated with each test material for 16 h. After pretreatment, the permeation of the model compound, nicotinamide, across membranes was measured and the results were compared to the flux across control membranes that were exposed to buffer alone. All

surfactants decreased skin barrier function to some extent. The degree of nicotinamide penetration enhancement was correlated with the ratio of the surfactant pretreatment concentration to the surfactant critical micelle concentration. The authors of the study suggested that solubilization of stratum corneum lipids may be an important mechanism explaining the effects observed.

The dermal uptake of cetyl betaine and lauryl betaine was measured in vivo with human skin.²³ Male volunteers received ¹⁴C-radiolabeled test materials in aqueous solution on the dorsal upper arm for 30 min. The concentrations of cetyl betaine and lauryl betaine applied were 0.14, 1.0, and 5.4 mM and 16, 100, and 800 mM, respectively. The positive control was 50 mM caffeine. At the end of the exposure period, the remaining test materials were rinsed from the skin and the skin was washed. The stratum corneum at the test sites were removed with repeated tape-stripping. Dermal uptake was assessed by measuring the recovered radioactivity from the tape strips and compared to predicted penetration values. The measured uptake of cetyl betaine and lauryl betaine was 28-160 nmol/cm² and 2.3-19.5 nmol/cm², respectively. The predicted penetration values were 51-292 nmol/cm² for cetyl betaine and 3.7-35 nmol/cm² lauryl betaine. Caffeine penetrated at expected amounts. The tape stripping indicated that the radiolabel was mostly found in the outer layers of the stratum corneum.

The same study also assessed skin barrier function using the same test concentrations for both test materials.²³ Non-radiolabeled cetyl betaine and lauryl betaine were applied to the skin for 30 min. The transepidermal water loss (TEWL) was assessed. No changes in TEWL values were observed after treatment of the skin with the betaines or with saline controls.

TOXICOLOGICAL STUDIES

Acute Toxicity

Acute toxicity studies are presented in Table 4. The oral LD₅₀ of betaine, cetyl betaine, lauryl betaine and C12-C14 alkyldimethyl betaines were 11.1 g/kg, 1.62 g/kg, 0.071 g/kg, and 3 ml/kg, respectively, in rats, and 2.64 g/kg for coco-betaine (30%) in a mouse study. Also in rats, the dermal LD₅₀ values were greater than 16 g/kg for cetyl betaine and 1.3 g/kg for lauryl betaine. The intravenous LD₅₀ of betaine in mice has been reported to be 0.83 g/kg bodyweight. The LD₅₀ values were 0.15 g/kg for cetyl betaine and 0.053 g/kg for lauryl betaine in an intraperitoneal study in rats.^{4,6,22}

Repeated Dose Toxicity

Repeated dose toxicity data are summarized in Table 5. No effects were observed at the highest dose tested for betaine in rats. No significant toxic effects were observed in rats that received up to 0.35 g/kg/day cetyl betaine in a 91-day oral study. The no observable effect level (NOEL) for coco-betaine was 250 mg/kg/day and the lowest observable effect level (LOEL) was 500 mg/kg/day in a 90-day oral study in rats when tested up to 500 mg/kg/day. In a study of C12-C14 alkyldimethyl betaines, systemic no observable adverse effects levels (NOAEL) were 50 mg/kg bw/day and 100 mg/kg bw/day in oral rat studies that tested the material up to 300 mg/kg/day and 1000 mg/kg/day, respectively. The systemic lowest observable adverse effects levels (LOAEL) for these 2 studies were 150 mg/kg bw/day (due to increased salivation, increased urea, and non-neoplastic histopathologic changes in the kidney and bladder) and 300 mg/kg bw/day (due to decreased food consumption, body weight gain, and absolute body weight), respectively.^{4,5,24}

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Reproductive and developmental toxicity studies are summarized in Table 6. Dermal reproductive and developmental toxicity studies of cetyl betaine in rabbits determined the maternal LOAEL to be 10 mg/kg/day due to decreased body weight gain and a maternal NOAEL could not be established. The developmental LOAEL was 40 mg/kg/day and the developmental NOAEL was 20 mg/kg/day. In oral reproductive and developmental toxicity studies of cetyl betaine in rats, the LOAEL for the dams was 50 mg/kg due to decreased body weight gain and a maternal NOAEL could not be calculated. The developmental LOAEL was 250 mg/kg and the developmental NOAEL was 150 mg/kg. In an oral C12-C14 alkyldimethyl betaines study, the reproductive NOEL was 150 mg/kg bw/day and the reproductive LOAEL was 300 mg/kg bw/day due to decreased pup weight and litter size and increased post-implantation loss and postnatal loss. Another oral C12-C14 alkyldimethyl betaines study determined the reproductive NOAEL to be 300 mg/kg/day when the test material was tested up to 1000 mg/kg/day.^{5,25,26}

CARCINOGENICITY

See repeated dose toxicity results in Table 5. Betaine was not carcinogenic when tested up to 5% in a 104-week dietary rat study.⁴

GENOTOXICITY

In vitro and in vivo genotoxicity studies are presented in Table 7. Betaine and C12-C14 alkyldimethyl betaines were not genotoxic in in vitro and in vivo studies.⁴⁻⁶

IRRITATION AND SENSITIZATION

Irritation and Anti-Irritation

Non-human and human irritation and anti-irritation studies are presented in Table 8. Betaine had anti-irritating effects on the skin in several efficacy studies in humans. In dermal studies, coco-betaine was not irritating in a rabbit study when tested at 16%, and was less irritating than sodium lauryl sulfate (SLS) in a human study at an unknown concentration. No dermal irritation reactions were observed in human studies of lauryl betaine at 0.1%, but were observed at concentrations of 1% and 10%. Dermal irritation results were mixed in rabbit studies of C12-C14 alkyldimethyl betaines, with irritation observed at 30% and at an unknown concentration in 2 studies, and no irritation was observed in 2 other studies at unknown concentrations. Betaine at 10% was not an ocular irritant in rabbits, nor were C12-C14 alkyldimethyl betaines at unknown concentrations in several rabbit studies; however, coco-betaine at 16% and 30% and lauryl betaine at 10% were ocular irritants. In human mucosal studies testing the efficacy of toothpaste, betaine did not produce adverse effects.^{1,4-6,27-30}

Sensitization

Non-human and human sensitization studies are presented in Table 9. Betaine (up to 50%), coco-betaine (up to 5%), lauryl betaine (0.1%), and C12-C14 alkyldimethyl betaines (up to 100%) were not sensitizing in non-human and human dermal studies.^{4-6,31,32}

Phototoxicity

No relevant published phototoxicity studies on alkyl betaines were discovered and no unpublished data were submitted.

CLINICAL USE

Case Reports

Coco Betaine

Two cases of eczematous lesions were reported following exposure to shampoos containing coco betaine.³³ In the first case, a 44-year old woman presented with acute eczematous lesions with erythema, edema, and vesiculation on the backs and palms of her hands a few days after using a shampoo with chestnut leaf extract. Her scalp also itched and was slightly red. Previous patch tests showed positive reactions to PPD, benzocaine, wool alcohols, parabens, chinosform, perfumes, nickel sulfate, and cobalt chloride. Patch tests with the shampoo and individual components showed a ++ reaction to the shampoo in open test as is and in patch test at 2% aq., ++ reaction to parahydroxybenzoic acid esters (5% pet.), and +++ reaction to coco betaine (2% aq.). No reactions were observed to the perfume component. The dermatitis cleared when the patient changed shampoos.

In the second case, a 22-year old woman presented with red, swollen face and weeping eczematous lesions. Red, oozing and crusted acute lesions were also observed on her shoulders and scalp. The symptoms occurred after using a new shampoo. Patch tests with the shampoo and the individual components showed a +++ reaction to the shampoo in open test as is and in patch test at 2% aq., ++ reaction to coco betaine (2% aq.), and ++ reaction to sodium lauryl ether sulfate (2% aq.). The symptoms cleared when the patient changed shampoos.³³

SUMMARY

The alkyl betaines are zwitterionic ingredients comprised of tertiary ammonium substituted acetate. These cosmetic ingredients mainly function as hair and skin conditioning agents. With the exception of betaine, alkyl betaines may also function as antistatic agents, surfactants-cleansing agents, and viscosity increasing agents. The common core chemical structure, similar functions and concentrations in cosmetics, and the expected bio-handling enabled grouping

these ingredients and reading across the available toxicological data to support the safety assessment of each individual compound in the entire group.

According to information supplied to FDA's VCRP, betaine has the most reported uses in cosmetic and personal care products, with a total of 459; the majority of the uses are in leave-on skin care preparations. Lauryl betaine has the second greatest number of overall uses reported, with a total of 338; the majority of those uses are in rinse-off personal cleanliness products. In an industry survey, betaine was reported to have a maximum use concentration range of 0.0001% to 8.7%, with the 8.7% reported in rinse-off non-coloring hair conditioner. Lauryl betaine was reported to have a maximum use concentration range of 0.015% to 8.8%, with 8.8% reported in rinse-off non-coloring hair shampoos.

Aside from use in cosmetics, betaine is a common food component and is used to treat homocystinuria.

Absorption and elimination of betaine in humans were dose dependent, with urinary excretion of betaine increasing with betaine dose.

Cetyl betaine and lauryl betaine were observed to decrease skin barrier function in hairless mouse skin in vitro. Cetyl betaine and lauryl betaine absorbed into mouse skin in vitro, with lauryl betaine absorbing at a faster rate. Dermal penetration rates, measured from the stratum corneum collected from tape stripping, for cetyl betaine and lauryl betaine were 51-292 nmol/cm² and 3.7-35 nmol/cm², respectively, in 30 min exposures to human skin in vivo.

The oral LD₅₀ of betaine, cetyl betaine, lauryl betaine and C12-C14 alkyldimethyl betaines were 11.1 g/kg, 1.62 g/kg, 0.071 g/kg, and 3 ml/kg, respectively, in rats, and 2.64 g/kg for coco-betaine (30%) in a mouse study. Also in rats, the dermal LD₅₀ values were greater than 16 g/kg for cetyl betaine and 1.3 g/kg for lauryl betaine. The intravenous LD₅₀ of betaine in mice has been reported to be 0.83 g/kg bodyweight. The LD₅₀ values were 0.15 g/kg for cetyl betaine and 0.053 g/kg for lauryl betaine in an intraperitoneal study in rats.

In repeated dose studies, no effects were observed at the highest dose tested (5%) for betaine in rats. No significant toxic effects were observed in rats that received up to 0.35 g/kg/day cetyl betaine in a 91-day oral study. The NOEL for coco-betaine was 250 mg/kg/day and the LOEL was 500 mg/kg/day in a 90-day oral study in rats when tested up to 500 mg/kg/day. In C12-C14 alkyldimethyl betaines, systemic NOAELs were 50 mg/kg bw/day and 100 mg/kg bw/day in oral rat studies that tested the material up to 300 mg/kg/day and 1000 mg/kg/day, respectively. The systemic LOAEL for these 2 studies were 150 mg/kg bw/day (due to increased salivation, increased urea, and non-neoplastic histopathologic changes in the kidney and bladder) and 300 mg/kg bw/day (due to decreased food consumption, body weight gain, and absolute body weight), respectively.

Dermal reproductive and developmental toxicity studies of cetyl betaine in rabbits determined the maternal LOAEL to be 10 mg/kg/day due to decreased body weight gain and a maternal NOAEL could not be established. The developmental LOAEL was 40 mg/kg/day and the developmental NOAEL was 20 mg/kg/day. In oral reproductive and developmental toxicity studies of cetyl betaine in rats, the LOAEL for the dams was 50 mg/kg due to decreased body weight gain and a maternal NOAEL could not be calculated. The developmental LOAEL was 250 mg/kg and the developmental NOAEL was 150 mg/kg. In an oral C12-C14 alkyldimethyl betaines study, the reproductive NOEL was 150 mg/kg bw/day and the reproductive LOAEL was 300 mg/kg bw/day due to decreased pup weight and litter size and increased post-implantation loss and postnatal loss. Another oral C12-C14 alkyldimethyl betaines study determined the reproductive NOAEL to be 300 mg/kg/day when the test material was tested up to 1000 mg/kg/day.

Betaine was not carcinogenic when tested up to 5% in a 104-week dietary rat study. Betaine and C12-C14 alkyldimethyl betaines were not genotoxic in in vitro and in vivo studies.

Betaine had anti-irritating effects on the skin in several efficacy studies in humans. In dermal studies, coco-betaine was not irritating in a rabbit study when tested at 16%, and was less irritating than SLS in a human study at an unknown concentration. No dermal irritation reactions were observed in human studies of lauryl betaine at 0.1%, but were observed at concentrations of 1% and 10%. Dermal irritation results were mixed in rabbit studies of C12-C14 alkyldimethyl betaines, with irritation observed at 30% and at an unknown concentration in 2 studies and no irritation observed in 2 other studies at unknown concentrations. Betaine at 10% was not an ocular irritant in rabbits, nor were C12-C14 alkyldimethyl betaines at unknown concentrations in several rabbit studies; however, coco-betaine at 16% and 30% and lauryl betaine at 10% were ocular irritants. In human mucosal studies testing the efficacy of toothpaste, betaine at 4% did not produce adverse effects.

Betaine (up to 50%), coco-betaine (up to 5%), lauryl betaine (0.1%, and C12-C14 alkyldimethyl betaines (up to 100%) were not sensitizing in non-human and human dermal studies.

Allergic reactions to coco-betaine have been reported in case reports.

DISCUSSION

The Panel considered the available data on alkyl betaines and noted the low systemic toxicity at high doses in single dose and repeated dose oral animal studies, no teratogenic or carcinogenic effects in animal studies, no genotoxicity in in vitro and in vivo studies, and no sensitization in multiple tests. The Panel noted that most surfactants exhibit some irritancy, as was noted in dermal and ocular studies of coco-betaine, lauryl betaine, and C12-C14 alkyldimethyl betaines. Thus the Panel stated that products that include these ingredients should be formulated to be non-irritating.

Although there are data gaps, the shared core chemical structure, similar functions and concentrations in cosmetics, and the expected similarities in physicochemical properties enabled grouping these ingredients and reading across the available toxicological data to support the safety assessment of each individual compound in the entire group.

The Panel noted that there were no data available on the UV absorption or phototoxicity of alkyl betaines; however, because none of the structures that comprise these ingredients are chromophores, the Panel felt that there was no concern that these ingredients would cause adverse effects from UV exposure.

The Panel expressed concern about animal-derived ingredients, namely the transmission of infectious agents. They stressed that these ingredients must be free of detectable pathogenic viruses or infectious agents (e.g., bovine spongiform encephalopathy (BSE)). These ingredients should be produced according to good manufacturing procedures and should conform to regulations for producing substances from animal-derived materials.

The Panel discussed the issue of incidental inhalation exposure from hairsprays, body and hand products, non-coloring hair powders, and indoor tanning preparations. There were no inhalation toxicity data available. Betaine is reportedly used at concentrations up to 3% in cosmetic products that may be aerosolized and up to 0.0001% in cosmetic products that may become airborne. The Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone, 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 eleven alkyl betaines listed below are safe in the present practices of use and concentration in cosmetics, when formulated to be non-irritating.

Behenyl Betaine

Betaine

Cetyl Betaine

Coco-Betaine

Decyl Betaine*

Hydrogenated Tallow Betaine*

Lauryl Betaine

Myristyl Betaine

Oleyl Betaine

Stearyl Betaine

Tallow Betaine*

*Not 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.

FIGURES**Figure 2.** Formulas and idealized structures of the ingredients in this safety assessment.

Betaine	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3 - \text{N}^+ - \text{CH}_2\text{COO}^- \\ \\ \text{CH}_3 \end{array}$
Behenyl Betaine	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3(\text{CH}_2)_{20}\text{CH}_2 - \text{N}^+ - \text{CH}_2\text{COO}^- \\ \\ \text{CH}_3 \end{array}$
Cetyl Betaine	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3(\text{CH}_2)_{14}\text{CH}_2 - \text{N}^+ - \text{CH}_2\text{COO}^- \\ \\ \text{CH}_3 \end{array}$
Coco-Betaine	$\begin{array}{c} \text{CH}_3 \\ \\ \text{R} - \text{N}^+ - \text{CH}_2\text{COO}^- \\ \\ \text{CH}_3 \end{array}$ <p>where R represents the alkyl groups derived from coconut oil. (wherein coconut is primarily comprised of capric (6-10%), lauric (44-52%), myristic (13-19%), and palmitic (8-11%) acids).³⁴</p>
Decyl Betaine	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3(\text{CH}_2)_8\text{CH}_2 - \text{N}^+ - \text{CH}_2\text{COO}^- \\ \\ \text{CH}_3 \end{array}$
Hydrogenated Tallow Betaine	$\begin{array}{c} \text{CH}_3 \\ \\ \text{R} - \text{N}^+ - \text{CH}_2\text{COO}^- \\ \\ \text{CH}_3 \end{array}$ <p>where R represents the alkyl groups derived from hydrogenated tallow (wherein tallow is primarily comprised of oleic (37-43%), palmitic (24-32%), stearic (20-25%), myristic (3-6%), and linoleic (2-3%) acids; and hydrogenation of tallow would result in the reduction of some of the unsaturated acids to saturated acids (i.e., increased stearic acid and decreased linoleic and oleic acids)).³⁵</p>
Lauryl Betaine	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3(\text{CH}_2)_{11} - \text{N}^+ - \text{CH}_2\text{COO}^- \\ \\ \text{CH}_3 \end{array}$
Myristyl Betaine	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3(\text{CH}_2)_{13} - \text{N}^+ - \text{CH}_2\text{COO}^- \\ \\ \text{CH}_3 \end{array}$
Oleyl Betaine	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_6 - \text{N}^+ - \text{CH}_2\text{COO}^- \\ \\ \text{CH}_3 \end{array}$
Stearyl Betaine	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3(\text{CH}_2)_{17} - \text{N}^+ - \text{CH}_2\text{COO}^- \\ \\ \text{CH}_3 \end{array}$
Tallow Betaine	$\begin{array}{c} \text{CH}_3 \\ \\ \text{R} - \text{N}^+ - \text{CH}_2\text{COO}^- \\ \\ \text{CH}_3 \end{array}$ <p>where R represents the alkyl groups derived from tallow (wherein tallow is primarily comprised of oleic (37-43%), palmitic (24-32%), stearic (20-25%), myristic (3-6%), and linoleic (2-3%) acids).³⁵</p>

TABLES**Table 1.** Definitions and functions of the ingredients in this safety assessment.² (The italicized text below represents additions made by CIR staff.)

Ingredient/CAS No.	Definition	Function
Betaine 107-43-7	Betaine is the zwitterion (inner salt) that conforms to the formula. <i>Betaine is the N,N,N-trimethylammonium zwitterion of glycine.</i>	Hair conditioning agents; humectants; skin-conditioning agents-humectants
Behenyl Betaine	Behenyl Betaine is the zwitterion (inner salt) that conforms to the formula. <i>Behenyl Betaine is the N-behenyl-N,N-dimethylammonium zwitterion of glycine.</i>	Antistatic agents; hair conditioning agents; skin-conditioning agents-misc.; surfactants-cleansing agents; surfactants-foam boosters; viscosity increasing agents-aqueous
Cetyl Betaine 693-33-4	Cetyl Betaine is the zwitterion (inner salt) that conforms to the formula. <i>Cetyl Betaine is the N-cetyl-N,N-dimethylammonium zwitterion of glycine.</i>	Antistatic agents; hair conditioning agents; skin-conditioning agents-misc.; surfactants-cleansing agents; surfactants-foam boosters; viscosity increasing agents-aqueous
Coco-Betaine 68424-94-2	Coco-Betaine is the zwitterion (inner salt) that conforms generally to the formula. <i>Coco-Betaine is the N-cocyl-N,N-dimethylammonium zwitterion of glycine.</i>	Antistatic agents; hair conditioning agents; skin-conditioning agents-misc.; surfactants-cleansing agents; surfactants-foam boosters; viscosity increasing agents-aqueous
Decyl Betaine 2644-45-3	Decyl Betaine is the zwitterion (inner salt) that conforms generally to the formula. <i>Decyl Betaine is the N-decyl-N,N-dimethylammonium zwitterion of glycine.</i>	Antistatic agents; hair conditioning agents; skin-conditioning agents-misc.; surfactants-cleansing agents; surfactants-foam boosters; viscosity increasing agents-aqueous
Hydrogenated Tallow Betaine	Hydrogenated Tallow Betaine is the zwitterion (inner salt) that conforms generally to the formula. <i>Hydrogenated Tallow Betaine is the ammonium zwitterion of glycine, wherein nitrogen is substituted with two methyl groups and a fatty chain derived from hydrogenated tallow.</i>	Antistatic agents; hair conditioning agents; skin-conditioning agents-misc.; surfactants-cleansing agents; surfactants-foam boosters; viscosity increasing agents-aqueous
Lauryl Betaine 683-10-3	Lauryl Betaine is the zwitterion (inner salt) that conforms generally to the formula. <i>Lauryl Betaine is the N-lauryl-N,N-dimethylammonium zwitterion of glycine.</i>	Antistatic agents; hair conditioning agents; skin-conditioning agents-misc.; surfactants-cleansing agents; surfactants-foam boosters; viscosity increasing agents-aqueous
Myristyl Betaine 2601-33-4	Myristyl Betaine is the zwitterion (inner salt) that conforms generally to the formula. <i>Myristyl Betaine is the N-myristyl-N,N-dimethylammonium zwitterion of glycine.</i>	Abrasives; antistatic agents; hair conditioning agents; skin-conditioning agents-misc.; surfactants-cleansing agents; surfactants-foam boosters; viscosity increasing agents-aqueous
Oleyl Betaine 871-37-4	Oleyl Betaine is the zwitterion (inner salt) that conforms generally to the formula. <i>Oleyl Betaine is the N-oleyl-N,N-dimethylammonium zwitterion of glycine.</i>	Antistatic agents; hair conditioning agents; skin-conditioning agents-misc.; surfactants-cleansing agents; surfactants-foam boosters; viscosity increasing agents-aqueous
Stearyl Betaine 820-66-6	Stearyl Betaine is the zwitterion (inner salt) that conforms to the formula. <i>Stearyl Betaine is the N-stearyl-N,N-dimethylammonium zwitterion of glycine.</i>	Antistatic agents; hair conditioning agents; skin-conditioning agents-misc.; surfactants-cleansing agents; surfactants-foam boosters; viscosity increasing agents-aqueous
Tallow Betaine	Tallow Betaine is the zwitterion (inner salt) that conforms generally to the formula. <i>Tallow Betaine is the ammonium zwitterion of glycine, wherein nitrogen is substituted with two methyl groups and a fatty chain derived from tallow.</i>	Antistatic agents; hair conditioning agents; skin-conditioning agents-misc.; surfactants-cleansing agents; surfactants-foam boosters; viscosity increasing agents-aqueous

Table 2. Physical and chemical properties.

	Property	Reference
<i>Betaine</i>		
Physical Form	Deliquescent scales or prisms	³⁶
Molecular Weight	117.15	^{6,36}
Melting Point	293 (decomposes)	⁶
Water Solubility g/L	160	³⁶
Other Solubility g/L	55 in methanol, 8.7 in ethanol, sparingly sol in ether	³⁶
<i>Cetyl Betaine</i>		
Vapor pressure mmHg@ 25 °C	2.4×10^{-12}	²⁵
Melting Point °C	243	²⁵
Boiling Point °C @ 760 mmHg	566	²⁵
Water Solubility mg/L @ 25 °C	171	²⁵
log K _{ow}	2.44	²⁵
<i>Lauryl Betaine</i>		
Physical Form	Crystals or colorless needles	³⁶
Molecular Weight g/mol	271.44	³⁶
Melting Point °C	183-185	³⁶
Water Solubility	Easily soluble in water	³⁶
Other Solubility	Easily soluble in methanol, ethanol, and benzene; moderately soluble in acetone	³⁶
Dissociation constants (pKa)	1.8	³⁶

Table 3. Frequency and concentration of use (2013) according to duration and type of exposure for alkyl betaines.^{10,11}

	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>
	Behenyl Betaine		Betaine		Cetyl Betaine	
Totals*	4	8.4	459	0.0001-8.7	14	0.36-7.4
Duration of Use						
Leave-On	1	NR	326	0.0001-8	NR	NR
Rinse-Off	3	8.4	130	0.09-8.7	14	0.36-7.4
Diluted for (Bath) Use	NR	NR	3	0.01	NR	NR
Exposure Type						
Eye Area	NR	NR	31	0.1-3	NR	NR
Incidental Ingestion	NR	NR	6	0.05-3	NR	NR
Incidental Inhalation-Spray	NR	NR	4	0.2-3 ^a	NR	NR
Incidental Inhalation-Powder	NR	NR	4	0.0001 ^b	NR	NR
Dermal Contact	4	8.4	379	0.01-6.5	12	0.36-7.4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	50	0.0001-8.7	2	NR
Hair-Coloring	NR	NR	22	0.44	NR	NR
Nail	NR	NR	NR	3	NR	NR
Mucous Membrane	NR	NR	19	0.01-3	6	0.36-7.4
Baby Products	NR	NR	4	NR	NR	NR
	Coco-Betaine		Lauryl Betaine		Myristyl Betaine	
Totals*	227	0.53-9.8	338	0.015-8.8	6	0.84
Duration of Use						
Leave-On	4	1.8-2	29	0.016-1.2	NR	NR
Rinse Off	213	0.53-9.8	281	0.015-8.8	6	0.84
Diluted for (Bath) Use	10	3.1-5.1	28	1	NR	NR
Exposure Type						
Eye Area	1	NR	2	0.016	NR	NR
Incidental Ingestion	NR	2	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	1	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	141	0.53-9.8	308	0.016-8	6	0.84
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	70	0.63-8	29	0.015-8.8	NR	NR
Hair-Coloring	16	1.5-2.3	1	0.19-3	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	87	2-5.1	262	0.75-4.2	6	0.84
Baby Products	3	NR	1	NR	NR	NR
	Oleyl Betaine		Stearyl Betaine			
Totals*	5	23.7	1	NR		
Duration of Use						
Leave-On	NR	NR	1	NR		
Rinse-Off	5	NR	NR	NR		
Diluted for (Bath) Use	NR	23.7	NR	NR		
Exposure Type						
Eye Area	NR	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	NR		
Incidental Inhalation-Spray	NR	NR	NR	NR		
Incidental Inhalation-Powder	NR	NR	NR	NR		
Dermal Contact	3	23.7	NR	NR		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	2	NR	1	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous Membrane	1	23.7	NR	NR		
Baby Products	NR	NR	NR	NR		

* 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.

NR = none reported

^a 0.5% in an aerosol hair spray, 3% in a pump hair spray, 0.2% in a body and hand spray.

^b 0.0001% in a powder non-coloring hair preparation.

Table 4. Acute toxicity studies in animals

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
<i>Oral</i>			
betaine anhydrous, > 97% pure; doses = 5, 10, 12.5, 15, 20 g/kg bw in water	OECD Guideline 401 for acute oral toxicity in Crj:CD(SD) rats; 5 rats of each sex per dose; GLP compliant	LD ₅₀ (calculated) = 11.1 g/kg bw in males and females; symptoms observed in each dose group included lethargy, decreased motor activity, prone posture, ataxia, musculature - tremor, bradypnea, hyperpnea, piloerection, ungroomed appearance, hunched posture and death	^{4,6}
cetyl betaine (94.9% pure) and lauryl betaine (98.9% pure) in 25% w/v solutions; doses not reported	Groups of 5 male Sprague-Dawley rats received either test material via oral gavage	LD ₅₀ = 1620 mg/kg for cetyl betaine and 71 mg/kg for lauryl betaine; symptoms in some animals for either test material were sluggishness, diarrhea, and lacrimation; weight gains were within normal parameters in surviving animals; gross necropsy of the animals that died during the study found the gastrointestinal tract distended with red fluid and lungs mottled and red; no significant differences in the pharmacotoxic signs or gross necropsy findings between the 2 test materials	²²
coco-betaine tested at 30% active ingredient and at 10% in water; doses = 6670, 8350, 10000 mg/kg bw	OECD Guideline 401 for acute oral toxicity in CF-1 mice; 10 mice per dose; not GLP compliant	LD ₅₀ (calculated) = 2640 mg/kg bw for 30% active ingredient and 8800 mg/kg bw for 10% in water	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine) in aqueous solution tested at 0, 1.6, 2.5, 3.2, 4.0, 5.0, 8.0 ml/kg bw	OECD Guideline 401 for acute oral toxicity in CFY rats; 5 rats of each sex per dose; not GLP compliant	LD ₅₀ (calculated) = 3 ml/kg bw in males and females; lethargy and diuresis observed at 3.2 ml/kg and greater; death preceded by ataxia and coma and occurred within 5-27 h post-dosing; total recovery in survivors 5 days post-dosing	⁵
<i>Dermal</i>			
cetyl betaine (94.9% pure) and lauryl betaine (98.9% pure); doses not reported	Groups of 5 male Sprague-Dawley rats received either test material dermally on clipped trunks; test sites were occluded for 24 h, after which the test sites were wiped clean of the test materials	LD ₅₀ = > 16 g/kg for cetyl betaine and 1.3 g/kg for lauryl betaine; erythema, edema, desquamation, necrosis, and scab formation observed on test sites for both test materials, as was sluggishness and reddish nasal and ocular discharges; body weight gains within normal parameters; no treatment-related changes due to either test material observed at gross necropsy	²²
<i>Intravenous/Intraperitoneal</i>			
betaine; no further details provided	Intravenous acute study in mice; no further details provided	LD ₅₀ = 830 mg/kg bw; no further details provided	⁶
cetyl betaine (94.9% pure) and lauryl betaine (98.9% pure) in 5% and 25% w/v solutions in distilled water; doses not reported	Groups of 5 male Sprague-Dawley rats received either test material intraperitoneally	LD ₅₀ = 150 mg/kg for cetyl betaine and 53 mg/kg for lauryl betaine; sluggishness, diarrhea, lacrimation, and distended abdomen observed in animals that received either test material; body weight gains within normal parameters; no treatment-related changes due to either test material observed at gross necropsy	²²

Table 5. Repeated dose toxicity in animals

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
betaine > 95% pure; doses = 0%, 1%, 2%, 5% in animal feed	OECD Guideline 407 for repeated dose 28-day oral toxicity in female Sprague-Dawley rats; number per dose not provided; GLP compliant	NOAEL > 5771 mg/kg bw/day; NOEL could not be derived due to high tolerance and reversibility of slight to moderate hepatocellular vacuolation effects in rats	4
betaine > 95% pure; tested up to 5% in animal feed	OECD Guideline 408 for repeated dose 90-day oral toxicity in male and female Sprague-Dawley rats; 20 rats of each sex per dose; GLP compliant	NOAEL and NOEL could not be determined due to high tolerance; slight hematology and hepatic changes that included increased liver weights, hepatocellular vacuolation, but no microscopic evidence of hepatotoxicity; no significant systemic signs of toxicity were observed in any treatment group during dosing	4
betaine > 99.9% pure; tested up to 5% in animal feed for both chronic and carcinogenicity studies	OECD Guideline 453 for combined chronic toxicity/carcinogenicity studies in male and female Fischer 344 rats; 52-week study had 10 rats of each sex per dose; 104-week study had 25 rats of each sex per dose;	NOEL determined for up to 5%, betaine was not carcinogenic; increased liver and kidney weights observed in both sexes in the 5% dose group; decrease in mean corpuscular volume and mean corpuscular hemoglobin observed; increased platelet count observed; minor effects in blood biochemistry for chronic study	4
cetyl betaine tested at 32% active adjusted to be delivered at doses of 0, 0.05, 0.15, 0.35 g/kg/day	91-day subchronic oral toxicity study in Sprague-Dawley rats; 10 rats of each sex per dose group; test material administered in feed; GLP compliant	All animals survived until end of treatment period; no treatment-related clinical observations; mean body weights and body weight gains significantly decreased in high dose males which was accompanied by significantly decreased total feed consumption – these observations were attributed to palatability problems of diet than toxic effects of test material; slight clinical chemistry changes observed in high dose animals; no gross or histologic alterations attributed to test material observed	24
coco-betaine tested at 29-33% active material in water at 0, 125, 250, and 500 mg/kg bw/day	OECD Guideline 408 for repeated dose 90-day oral toxicity in male and female Sprague-Dawley rats; 10 rats of each sex per dose; GLP compliant	NOEL = 250 mg/kg bw/day; LOEL = 500 mg/kg bw/day due to increased water consumption. Irritative effects observed in the forestomach of mid and high dose group, possibly due to gavage dosing. No adverse effects on reproductive organs.	5
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine) in water at 0, 50, 150, 300 mg/kg bw/day	OECD Guideline 422 for combined repeated dose oral toxicity study with reproduction/developmental toxicity screening test in male and female Wistar rats; 10 rats of each sex per dose; GLP compliant	NOAEL (systemic) = 50 mg/kg bw/day; LOAEL (systemic) = 150 mg/kg bw/day due to increased salivation, increased urea, and non-neoplastic histopathologic changes in the kidney and bladder; NOEL (reproduction) = 150 mg/kg bw/day; LOAEL (reproduction) = 300 mg/kg bw/day due to pup weight, litter size, post-implantation loss, and postnatal loss.	5
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine) in water at 0, 33, 100, 300, and 1000 mg/kg bw/day	OECD Guideline 422 for combined repeated dose oral toxicity study with reproduction/developmental toxicity screening test in male and female Wistar rats; 3 rats of each sex per dose; not GLP compliant	NOAEL (systemic) = 100 mg/kg bw/day; LOAEL (systemic) = 300 mg/kg bw/day due to decreased food consumption, body weight gain, and absolute body weight; no reproductive results reported due to small group sizes.	5

Table 6. Reproductive and developmental toxicity

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine); 0, 50, 150, or 300 mg/kg bw/day active ingredient in water	OECD Guideline 422 for combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in male and female Wistar rats by oral gavage; 10 animals per sex per dose; males dosed 4 weeks, females dosed 7 weeks; GLP compliant	In parental animals, sedation, salivation, and irritation effects in the stomach and bladder due to the irritating nature of the test material were observed in the high dose group. Additionally, reduced weight gain and reduced absolute body weights were observed in the high dose group and in the mid dose group, but in a milder form. Reduced pup weight, litter size, and increased post-implantation and postnatal loss were observed in the high dose group and were considered secondary to maternal toxicity. No adverse effects were observed in the low dose group and their offspring.	5
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine); 0, 33, 100, 300, or 1000 mg/kg bw/day in water	OECD Guideline 422 for combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in male and female Wistar rats by oral gavage; 3 animals per sex per dose; males dosed 4 weeks, females dosed 6 weeks; not GLP compliant	All parental animals in the 1000 mg/kg/day dose group died within 24 h of the first dose. At 300 mg/kg/day, no adverse effects on reproduction were observed. The NOAEL of the test substance for reproduction was 300 mg/kg/day.	5
cetyl betaine; 0, 10, 20, 40, 100, or 200 mg/kg/day in 5% isopropanol in dosages of 2 ml/kg.	Dermal development toxicity/teratogenicity study in female New Zealand White rabbits. Groups of 8 artificially inseminated rabbits received the test material for 4 hours daily on approximately days 6 through 18 of gestation. Test substance-related mortality and severe topical effects occurred in the 100 and 200 mg/kg dose groups after the eighth and sixth dosages, respectively, and administration of these dose levels was discontinued. Two additional test groups (n=8 each) of non-inseminated rabbits were added: one received a new vehicle control (not reported) and the other received 2 mg/kg/day of the test material in the new vehicle control. All animals were observed daily for signs of toxicity, skin irritation, abortion (inseminated rabbits), death, body weight and feed consumption. Rabbits that died during the study were examined for pregnancy (inseminated rabbits) and cause of death. The inseminated rabbits were killed on day 19 of gestation and the non-inseminated rabbits were killed 24 h after the 13 th daily dosage was administered. Inseminated rabbits underwent a complete gross necropsy, including examination of the brain, uterus, and fetuses.	Maternal LOAEL = 10 mg/kg/day; maternal NOAEL could not be established; developmental LOAEL = 40 mg/kg/day; developmental NOAEL = 20 mg/kg/day. In the 100 and 200 mg/kg dose groups, 3 rabbits each died or were killed during the course of the study. Clinical observations in these groups and the 40 mg/kg dose group included uncoordinated movement, partial paralysis, red exudate of vaginal origin present in the cage pan, green matted fur, ataxia, and alopecia. All skin reactions, including erythema, desquamation, atonia, fissuring, eschar and exfoliation were dose-dependent. All rabbits in each dose group had a minimum of grade 1 erythema observed at least once. No rabbits in any dose group had edema. When compared to the control group, average body weight gain was inhibited in rabbits of the 2 through 200 mg/kg dose groups and was considered to be dose dependent. The severity of the effect was slight in the 2 and 10 mg/kg dose groups and marked in the 100 and 200 mg/kg dose groups. Decreased average daily feed consumption was noted in the 2 through 200 mg/kg dose groups and was also considered to be dose dependent. It was considered biologically significant in the 40 to 200 mg/kg dose groups. Pregnancy was observed in 6 or 7 of the 8 rabbits in each dose group. An increased incidence of resorptions was observed in the maternally toxic doses of 40, 100, and 200 mg/kg/day. A decrease in average litter size was observed in the 100 and 200 mg/kg dose groups. All fetuses were alive at Caesarean-sectioning, but were not examined and no further data about the fetuses are available. The results determined that doses of 0, 2, 10, and 20 mg/kg would be used in a definitive rabbit teratology study (results of this study have not been found).	25,26

Table 6. Reproductive and developmental toxicity

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
cetyl betaine; received 0, 50, 150, and 250 mg/kg /day of 30.4% active cetyl betaine in 10% ethanol (correction factor of 3.2895 was utilized to achieve proper amount of active ingredient)	Oral developmental toxicity/teratogenicity study, female Sprague-Dawley rats. ^{25,26} The control group received ethanol in deionized water at a volume of 5 ml/kg, which was the same amount of ethanol that the 250 mg/kg cetyl betaine dose group received. The rats received the test material daily for 10 days starting on gestation day 6. The animals were observed twice daily for signs of toxicity and body weights and feed consumption were recorded on day 0, 6, 9, 12, 16, and 20 of gestation. On gestation day 20, all surviving rats were killed and the uterus and the fetuses were examined and measured for number and location of viable and nonviable fetuses, early and late resorptions, number of total implantations and corpora lutea, fetal body weights, sex, external malformations or developmental variations, and skeletal abnormalities.	Maternal LOAEL = 50 mg/kg based on the inhibited body weight gain; maternal NOAEL could not be established; developmental LOAEL = 250 mg/kg; developmental NOAEL = 150 mg/kg. No mortalities observed in any of the dams in the control or treatment groups. In the 250 mg/kg dose group, clinical observations included stained and matted fur primarily on the limbs, neck, ventral thorax, and facial area, excessive salivation, respiratory rales, diarrhea, decreased activity, hypothermia, lacrimation, labored breathing, and wheezing. Similar observations were made in the 150 mg/kg dose group, with the stained and matted fur and respiratory rales the predominant signs of toxicity. Inhibition of maternal body weight gain was observed as a dose-related trend during overall gestation and the treatment periods at all dose levels. Weight loss was observed during the first treatment interval in the 150 and 250 mg/kg dose groups. Decreased feed consumption was also observed in all treated groups during the treatment period in a dose-dependent manner. Feed consumption was noted to be inhibited at 250 mg/kg during the overall gestation period, but the mean values for the 50 and 150 mg/kg dose groups were comparable to controls. In the fetuses, no significant differences between the control and treated groups were evident with respect to number of corpora lutea, total implantations, post implantation loss, viable fetuses, and fetal body weights. Fetal malformation in the treated groups was not significantly different from that of the controls. Reduced or absent ossification of the skull, sternebrae #5 and/or #6, and other sternebrae occurred more frequently in the 250 mg/kg dose group. These effects were considered to be biologically significant as they were observed in conjunction with reduced maternal body weight gains. No other developmental variations were noted.	25,26

Table 7. Genotoxicity

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
<i>In Vitro</i>			
betaine monohydrate > 95% pure; concentrations up to 10 mg/ml with and without S9 metabolic activation	Chromosome aberration study using human lymphocytes in whole blood cultures with and without metabolic activation; GLP compliant	Not clastogenic	4,6
betaine monohydrate > 97% pure; concentrations plated = 8 to 5000 µg/plate with and without S-9 activation	Bacterial reverse mutation assay using <i>Salmonella typhimurium</i> strains TA98, TA100, TA1535, TA1537 with and without S-9 metabolic activation; GLP compliant	Not genotoxic	4,6
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine); up to 5.0 mg/plate with and without S9 metabolic activation	OECD Guideline 471 for bacterial reverse mutation (Ames) assay in <i>Salmonella typhimurium</i> strains TA97a, TA98, TA100, TA1535, TA102 with and without metabolic activation; GLP compliant	Not genotoxic with or without metabolic activation.	5
alkyl dimethyl betaine (no further description) 30.2% active ingredient; up to 100 µg/ml with S9 and up to 75 µg/ml without S9	OECD Guideline 476 for in vitro mammalian cell gene mutation test in Chinese hamster ovary (CHO) cells – HGPRT locus with and without metabolic activation; GLP compliant	Not genotoxic with or without metabolic activation	5
alkyl dimethyl betaine (no further description) 30% active ingredient; up to 200µg/ml without S9 with 4 h exposure, up to 100 µg/ml without S9 with 20 h exposure, and up to 150 µg/ml with S9	OECD Guideline 473 for in vitro mammalian chromosome aberration test in CHO cells with and without metabolic activation; GLP compliant	Not genotoxic with or without metabolic activation	5
<i>In Vivo</i>			
betaine monohydrate > 98% pure; doses = 0, 0.5, 1, or 2 g/kg in saline	OECD Guideline 474 for mammalian erythrocyte micronucleus test using male and female CD-1 mice; test material or the positive control cyclophosphamide administered by gavage; exposure periods were 24, 48, or 72 h; GLP compliant.	Micronuclei were not induced in the bone marrow of mice dosed up to 2 g/kg	4,6

Table 8. Irritation and anti-irritation studies

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
<i>Dermal – Non-Human</i>			
coco-betaine tested at 16% in solution	OECD Guideline 404 for acute dermal irritation/corrosion in 3 albino rabbits; occlusive on shaved and abraded skin	Mean erythema score = 0.5/4, fully reversible within 24 h; mean edema score = 0.5/4, fully reversible within 24 h. Not irritating.	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine) tested as 30% active material neat	OECD Guideline 404 for acute dermal irritation/corrosion in 3 New Zealand White rabbits; semioclusive on shaved skin; GLP compliant	Very slight to slight edema between 30 min and 72 h post-dosing. Very slight to moderate erythema up to day 7. Skin was dry, rough and had fine to coarse scales with desquamation. Effects fully reversible within 14 days. Classified as irritating.	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine), concentration not reported	OECD Guideline 404 for acute dermal irritation/corrosion in 6 New Zealand White rabbits; occlusive on shaved skin; not GLP compliant	Mean erythema score = 1.83/4, not fully reversible within 72 h Mean edema score = 0.83/4, not fully reversible within 72 h Not irritating.	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine), concentration not reported	OECD Guideline 404 for acute dermal irritation/corrosion in 6 New Zealand White rabbits; occlusive on shaved skin; GLP compliant	Mean erythema score = 1.17/4, not fully reversible within 7 days Mean edema score = 0.72/4, not fully reversible within 7 days Not irritating.	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine), concentration not reported	OECD Guideline 404 for acute dermal irritation/corrosion in 6 New Zealand White rabbits; occlusive on shaved skin; not GLP compliant	Mean erythema score = 1.83/4, not fully reversible within 72 h Mean edema score = 1.08/4, not fully reversible within 72 h Moderate irritant.	⁵
<i>Dermal - Human</i>			
betaine; tested up to 10%	Efficacy study of test material in reducing irritation in soap was assessed in 2 studies with healthy subjects (n=28 and n=21)	Soap containing betaine found to be less irritating than those without the test material, but not in a dose-dependent manner	^{1,27}
betaine; tested up to 5% in several vehicles	Acute dermal irritation/corrosion study in 26 healthy volunteers; 2 occlusive Finn patches for 2 consecutive 24 h periods; test site area = 50 mm ²	Not irritating; some anti-irritancy observed with some of the vehicles	⁴
betaine; > 95% pure tested at 3.5% with 2% sodium lauryl sulfate (SLS) in water	20 male and 20 female test subjects with test products applied on permuated test areas on different arms inside of the crook of the elbow for 4 weeks; test areas washed and measurement of transepidermal water loss (TEWL) was measured after 4 weeks and 6 hours after the last washing; signs of irritation were observed at the end of the test and test areas were assessed for erythema, flaking, roughness, pruritus and formation of papules	Betaine found to lessen irritation effects of SLS and considered anti-irritating	⁴
coco-betaine in distilled water	Potential of 4 surfactants, including coco-betaine, to cause dermal irritation was assessed in a TEWL study with Finn chambers in 27 healthy volunteers; 24 h exposure	Sodium lauryl sulfate (SLS) had greatest mean TEWL (15.5 g/m ² h), followed by coco-betaine (12.6 g/m ² h), sodium laurate (10.6 g/m ² h), and polysorbate-60 (9.8 g/m ² h); no severe irritation (3+ or 4+) was observed following the exposure to 2 g/100 ml of the test substances (the mean overall scores for coco-betaine and SLS were 1.03 and 1.833, respectively); coco-betaine had less irritation potential than SLS	²⁸
lauryl betaine at 0.1% active ingredient	Acute dermal irritation in 19 human subjects; not occluded; 30 h exposure	No reactions observed.	⁵
lauryl betaine at 1% and 10% active ingredient	Acute dermal irritation in 7 human subjects; occluded; 24 h exposure	10% solution had 1 strong erythema, 4 moderate, and 2 mild; 1% solution had 5 strong erythema, 1 moderate and 1 mild.	⁵
<i>Ocular– Non-Human</i>			
betaine monohydrate > 95% pure; 10% w/v in distilled water	OECD Guideline 405 for acute ocular irritation/corrosion in albino rabbits; GLP compliant no further details were provided	Not irritating	^{4,6}
coco-betaine tested at 16% solids with no vehicle	OECD Guideline 405 for acute ocular irritation/corrosion in 3 albino rabbits; unwashed eyes; not GLP compliant	Test material caused corneal involvement and conjunctival irritation that did not clear by day 7 post-dosing. Irritating.	⁵
coco-betaine tested at 30% active material with no vehicle	OECD Guideline 405 for acute ocular irritation/corrosion in 3 albino rabbits; unwashed eyes; not GLP compliant	Test material caused corneal and iris involvement and conjunctival irritation that did not clear by day 7 post-dosing. Irritating.	⁵
lauryl betaine tested at 10% (v/v) solution in distilled water	OECD Guideline 405 for acute ocular irritation/corrosion in 3 New Zealand White rabbits; unwashed eyes; GLP compliant	Irritating.	⁵

Table 8. Irritation and anti-irritation studies

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine), concentration not reported	OECD Guideline 405 for acute ocular irritation/corrosion in 9 New Zealand White rabbits; washed and unwashed eyes; not GLP compliant	Mean cornea score = 0/4; mean iris score = 0.11/2, fully reversible within 72 h; mean conjunctivae score = 0.78/4, not fully reversible within 72 h; mean chemosis score = 0.17/4, fully reversible within 72 h. Not irritating.	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine), concentration not reported	OECD Guideline 405 for acute ocular irritation/corrosion in 9 New Zealand White rabbits; washed and unwashed eyes; not GLP compliant	Mean cornea score = 0.83/4, not fully reversible within 72 h; mean iris score = 0.55/2, not fully reversible within 72 h; mean conjunctivae score = 1.33/3, not fully reversible within 72 h; mean chemosis score = 0.72/4, not fully reversible within 72 h. Not irritating.	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine), concentration not reported	OECD Guideline 405 for acute ocular irritation/corrosion in 6 New Zealand White rabbits; unwashed eyes; GLP compliant	Mean cornea score = 0.22/4, fully reversible within 72 h; mean iris score = 0.55/2, not fully reversible within 72 h; mean conjunctivae score = 1.33/3, not fully reversible within 72 h; mean chemosis score = 0.83/4, not fully reversible within 72 h. Not irritating.	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine), concentration not reported	OECD Guideline 405 for acute ocular irritation/corrosion in 6 New Zealand White rabbits; unwashed eyes; GLP compliant	Mean cornea score = 0/4; mean iris score = 0.11/2, fully reversible within 48 h; mean conjunctivae score = 0.78/3, fully reversible within 72 h; mean chemosis score = 0.28/4, fully reversible within 72 h. Not irritating.	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine), concentration not reported	OECD Guideline 405 for acute ocular irritation/corrosion in 9 New Zealand White rabbits; washed and unwashed eyes; not GLP compliant	Mean cornea score = 0.22/4, fully reversible within 72 h; mean iris score = 0.22/2, fully reversible within 72 h; mean conjunctivae score = 1.16/3, not fully reversible within 72 h; mean chemosis score = 0.33/4, not fully reversible within 72 h. Not irritating.	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine), concentration not reported	OECD Guideline 405 for acute ocular irritation/corrosion in 9 New Zealand White rabbits; washed and unwashed eyes; not GLP compliant	Mean cornea score = 0.61/4, not fully reversible within 72 h; mean iris score = 0.22/2, not fully reversible within 72 h; mean conjunctivae score = 1.44/3, not fully reversible within 72 h; mean chemosis score = 0.72/4, not fully reversible within 72 h. Not irritating.	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine), concentration not reported	OECD Guideline 405 for acute ocular irritation/corrosion in 6 New Zealand White rabbits; unwashed eyes; GLP compliant	Mean cornea score = 0/4; mean iris score = 0.28/2, fully reversible within 72 h; mean conjunctivae score = 1.05/3, not fully reversible within 72 h; mean chemosis score = 0.72/4, fully reversible within 72 h. Not irritating.	⁵
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine), concentration not reported	OECD Guideline 405 for acute ocular irritation/corrosion in 9 New Zealand White rabbits; washed and unwashed eyes; GLP compliant	Mean cornea score = 0.06/4, fully reversible in 48 h; mean iris score = 0.16/2, fully reversible within 48 h; mean conjunctivae score = 0.67/3, fully reversible within 72 h; mean chemosis score = 0.22/4, fully reversible within 72 h. Not irritating.	⁵
<i>Mucosal – Human</i>			
betaine at 4% in a toothpaste	Study of the effects of betaine to reduce mucosal irritation in toothpastes containing SLS in 20 subjects; subjects exposed to the test materials on buccal mucosa with a test chamber kept in place for 15 min. Irritation was assessed visually and with electrical impedance for up to 45 min	Toothpaste containing 4% betaine alone did not irritate the mucosa in vivo; toothpastes that contained SLS, including those with betaine, were observed to have irritating effects on the oral mucosa.	²⁹
betaine at 4% in a toothpaste	Study testing the efficacy of betaine to reduce “dry mouth” in toothpaste with SLS using 13 subjects	No adverse effects to the toothpaste containing 4% betaine	³⁰

Table 9. Dermal sensitization studies.

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
<i>Non-Human</i>			
betaine monohydrate > 97% pure; up to 50% tested for induction and challenge	OECD Guideline 406 for skin sensitization – guinea pig maximization test in female Dunkin-Hartley guinea pigs; groups of 10 animals; GLP compliant	Not sensitizing	4,6
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine); 5%, 10%, 25%, 50% (w/v) in ethanol/water (7/3, v/v), and 100%	OECD Guideline 429 for LLNA in CBA mice; 4 mice per dose; GLP compliant	Stimulation indices (SI) = 2.4 (5%), 6.2 (10%), 14.7 (25%), 19.0 (50%), and 26.0 (100%). EC3 = 5.8% w/v. Slight (at 10%) to severe (at 100%) erythema observed upon second application. Not sensitizing.	5
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine); 0.1% of 30% active material	Draize test in 6 male Dunkin-Hartley guinea pigs	Not sensitizing	5
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine); 5% for induction, 1% for challenge; water vehicle	OECD Guideline 406 for skin sensitization – Buehler test in 20 female Himalayan spotted guinea pigs with 10 control animals; GLP compliant	No mortalities or signs of systemic toxicity. No skin effects observed in 1 st and 2 nd week of induction. Discrete/patchy to moderate confluent erythema (grade 1 and 2) observed in 12/20 animals in 3 rd week of induction. Not sensitizing.	5
betaines, C12-14-alkyldimethyl (a mixture of lauryl betaine and myristyl betaine); 0.5% (w/w) intradermal induction, 25% (w/w) epicutaneous induction, 1% (w/w) challenge	OECD Guideline 406 for skin sensitization – Magnusson and Kligman guinea pig maximization test in 10 male and 10 female Hartley guinea pigs; 5 of each sex for control; GLP compliant	Irritation reactions observed. Discrete erythema (grade 1) in 5/20 at 24 h post-challenge. Moderate erythema (grade 2) in 2/20 at 48 h post-challenge. Not sensitizing.	5
coco-betaine; 0.5% intradermal induction, 5% epicutaneous induction, 1% challenge	OECD Guideline 406 for skin sensitization – guinea pig maximization test in female Dunkin-Hartley guinea pigs ; 10 animals/dose; GLP compliant	Not sensitizing	5
<i>Human</i>			
betaine at 8.7% in a fragrance-free white lotion/moisturizer; tested neat	Human repeat insult patch test (HRIPT) in 102 subjects; semi-occluded patches consisted of 2 cm ² Webril pads with 0.2 ml of the test material and were applied to the infrascapular area of the back or to the upper arm	Not sensitizing	31
betaine at 5% in a leave-on product	HRIPT in 51 subjects; occlusive; subjects received on their backs 0.2 ml of the test material with Parke-Davis Readi-Bandage® (approximately 0.05 ml/cm ²)	No skin irritation or allergic contact dermatitis	32
lauryl betaine at 0.1% active ingredient	HRIPT in 20 volunteers; occlusive	One strong reaction in volunteer after day 6 of induction and a mild reaction in another volunteer after day 7. No reactions observed immediately after challenge. Four delayed reaction observed during the next 4 days with 1 strong, 1 moderate, and 2 mild in form. Reactions were considered due to primary irritation and not to sensitization.	5

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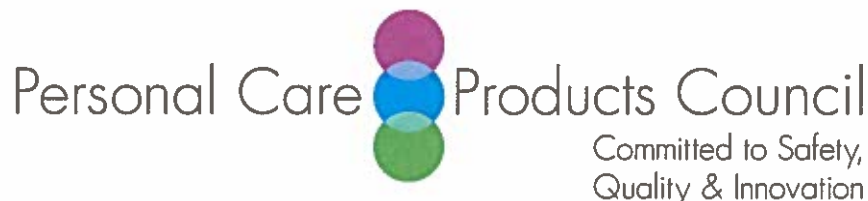
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2013 VCRP Raw Data

12A - Cleansing	BEHENYL BETAINE	3
12C - Face and Neck (exc shave)	BEHENYL BETAINE	1
01B - Baby Lotions, Oils, Powders, and Creams	BETAINE	4
02D - Other Bath Preparations	BETAINE	3
03D - Eye Lotion	BETAINE	13
03E - Eye Makeup Remover	BETAINE	3
03F - Mascara	BETAINE	2
03G - Other Eye Makeup Preparations	BETAINE	13
05A - Hair Conditioner	BETAINE	15
05C - Hair Straighteners	BETAINE	1
05F - Shampoos (non-coloring)	BETAINE	15
05G - Tonics, Dressings, and Other Hair Grooming Aids	BETAINE	12
05H - Wave Sets	BETAINE	1
05I - Other Hair Preparations	BETAINE	6
06B - Hair Tints	BETAINE	22
07E - Lipstick	BETAINE	6
07F - Makeup Bases	BETAINE	4
07I - Other Makeup Preparations	BETAINE	4
10A - Bath Soaps and Detergents	BETAINE	8
10E - Other Personal Cleanliness Products	BETAINE	2
11A - Aftershave Lotion	BETAINE	1
12A - Cleansing	BETAINE	46
12C - Face and Neck (exc shave)	BETAINE	90
12D - Body and Hand (exc shave)	BETAINE	12
12F - Moisturizing	BETAINE	109
12G - Night	BETAINE	10
12H - Paste Masks (mud packs)	BETAINE	17
12I - Skin Fresheners	BETAINE	10
12J - Other Skin Care Preps	BETAINE	26
13B - Indoor Tanning Preparations	BETAINE	2
13C - Other Suntan Preparations	BETAINE	2
05F - Shampoos (non-coloring)	CETYL BETAINE	2
10A - Bath Soaps and Detergents	CETYL BETAINE	3
10E - Other Personal Cleanliness Products	CETYL BETAINE	3
12A - Cleansing	CETYL BETAINE	6
01A - Baby Shampoos	COCO-BETAINE	3
02A - Bath Oils, Tablets, and Salts	COCO-BETAINE	1
02B - Bubble Baths	COCO-BETAINE	7
02D - Other Bath Preparations	COCO-BETAINE	2
03E - Eye Makeup Remover	COCO-BETAINE	1
05A - Hair Conditioner	COCO-BETAINE	1
05D - Permanent Waves	COCO-BETAINE	2
05F - Shampoos (non-coloring)	COCO-BETAINE	62
05I - Other Hair Preparations	COCO-BETAINE	2
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	COCO-BETAINE	14

06D - Hair Shampoos (coloring)	COCO-BETAINE	2
10A - Bath Soaps and Detergents	COCO-BETAINE	67
10E - Other Personal Cleanliness Products	COCO-BETAINE	10
11E - Shaving Cream	COCO-BETAINE	4
12A - Cleansing	COCO-BETAINE	47
12D - Body and Hand (exc shave)	COCO-BETAINE	1
12J - Other Skin Care Preps	COCO-BETAINE	1
01C - Other Baby Products	LAURYL BETAINE	1
02A - Bath Oils, Tablets, and Salts	LAURYL BETAINE	1
02B - Bubble Baths	LAURYL BETAINE	12
02D - Other Bath Preparations	LAURYL BETAINE	15
03D - Eye Lotion	LAURYL BETAINE	1
03E - Eye Makeup Remover	LAURYL BETAINE	1
05A - Hair Conditioner	LAURYL BETAINE	1
05F - Shampoos (non-coloring)	LAURYL BETAINE	27
05I - Other Hair Preparations	LAURYL BETAINE	1
06D - Hair Shampoos (coloring)	LAURYL BETAINE	1
10A - Bath Soaps and Detergents	LAURYL BETAINE	36
10E - Other Personal Cleanliness Products	LAURYL BETAINE	198
11E - Shaving Cream	LAURYL BETAINE	1
12A - Cleansing	LAURYL BETAINE	16
12C - Face and Neck (exc shave)	LAURYL BETAINE	13
12D - Body and Hand (exc shave)	LAURYL BETAINE	5
12F - Moisturizing	LAURYL BETAINE	1
12J - Other Skin Care Preps	LAURYL BETAINE	6
13B - Indoor Tanning Preparations	LAURYL BETAINE	1
10A - Bath Soaps and Detergents	MYRISTYL BETAINE	3
10E - Other Personal Cleanliness Products	MYRISTYL BETAINE	3
05A - Hair Conditioner	OLEYL BETAINE	1
05F - Shampoos (non-coloring)	OLEYL BETAINE	1
10E - Other Personal Cleanliness Products	OLEYL BETAINE	1
12A - Cleansing	OLEYL BETAINE	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	STEARYL BETAINE	1



Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: December 5, 2013

SUBJECT: Comments on the Draft Report on Betaine and Alkyl Betaines Prepared for the December 2013 CIR Expert Panel Meeting

Key Issue

As the European Chemicals Agency (ECHA) did not write the study summaries included in the dossier for this ingredient, they should not be listed as the "author" in the reference section. ECHA is the source, rather than the author of this information.

The substitution of a long chain alkyl group for a methyl group of Betaine modifies the properties of these compounds and influences how these compounds are used in cosmetics.

Therefore, as an acknowledgment of the differences between Betaine and the other alkyl betaine compound, it would be more appropriate to call this report "Safety Assessment of Betaine and Alkyl Betaines as Used in Cosmetics", and to refer to the compounds included in the report and "Betaine and 10 alkyl betaines".

Additional Comments

Impurities - Please provide a reference for "Trace analysis show very small amounts of PCB, PAH and dioxins." If the levels of these substances were all less than the detection limit of the analytical methods, it is misleading to imply that these substances were actually found.

Toxicological Studies, Reproductive and Developmental Studies, Carcinogenicity, Irritation and Anti-Irritation - Please provide references for these sections when the text discusses a specific study. Without references in the text it is difficult to refer to the table and find the additional details about the same study.

Toxicological Studies, Repeated Dose Exposure - It is misleading to state that the "No observable effects levels (NOEL) could not be determined for betaine due to the high tolerance of this ingredient in rats." It would be more appropriate to indicate that no effects were observed at the highest dose tested. This NOEL would be considered a free-

standing NOEL as no adverse effects were observed. Please correct the structure of the sentence that starts with: "In coco-betaine, the NOEL was..." - presumably the NOEL was from a study of Coco-betaine.

Carcinogenicity - Please indicate that the carcinogenicity study was a dietary study.

Summary - What were the dermal penetration rates of Cetyl Betaine and Lauryl Betaine in human skin? In the Summary it is misleading to state that the "No observable effects levels (NOEL) could not be determined for betaine due to the high tolerance of this ingredient in rats." It would be more appropriate to indicate that no effects were observed at the highest dose tested. "In coco-betaine..." also needs to be corrected in the Summary. The Summary should state what happened to "pup weight, litter size, post-implantation loss, and postnatal loss" at the LOAEL of 300 mg/kg/day. Please indicate that the cancer study was a dietary study.


Table 5, 104 week study - Please correct: "live and kidney weights"

Table 6, last entry - NOAELs and LOAELs are generally actual doses used in the study (they do not need to be calculated). Therefore, it is not appropriate to state: "maternal NOAEL could not be calculated"



Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel 

DATE: January 10, 2014

SUBJECT: Comments on the Tentative Report on Betaine and Alkyl Betaines

Key Issue

Somewhere in this CIR report, it would be helpful if there was a clear acknowledgment that there is a difference in chemical properties and function in cosmetic products of Betaine compared to the rest of the ingredients in the report. For example, in the Introduction, rather than stating that these ingredients "mainly function as antistatic agents...", it would be more accurate to state: "With the exception of Betaine, antistatic agent is a function listed for the alkyl betaine ingredients."

Additional Comments

Throughout the report, rather than saying "a betaine analog", please just state the compound, e.g., C12-14 alkyldimethyl betaine.

- p.2 - As only 3 ingredients are shown in Table 3, how is it known that "Most of these ingredients are colorless, crystalline materials with good solubility in water and polar organic solvents." Please add a reference for this sentence? Which of the ingredients do not fit these criteria (is the word "most" needed)?
- p.4 - In the description of reference 21, rather than stating "dose-dependent effect" please be more specific, e.g., "dose-dependent increase".
- p.4 - In the description of reference 22, it is no clear what is meant by "well absorbed (approximately 50% within 24 h)". Does this mean that 50% was recovered in the receptor fluid, or was 50% the amount that was recovered in the receptor fluid plus skin?
- p.5 - Please correct the structure of the following phrase: "In a betaine analog,...". Presumably, this should be: "In a study of C12-14 alkyldimethyl betaine,..."
- p.7 - As the Summary is presented without the rest of the report when it is presented in the Compendium, the Summary should also note that Betaine is a common food component and that it is used to treat homocystinuria.

- p.7 - Please clarify what is represented by “dermal penetration”. Is this the amount recovered in the receptor fluid, or the amount recovered in the receptor fluid and skin?
- p.7 - What was the highest dose of Betaine tested in rats in repeated dose studies?
- p.7 - What concentration of Betaine was in the toothpaste in the mucosal irritation studies?
- p.7 - It is not necessary to refer to a table (Table 9) in the Summary.
- p.7 - Unless exposure was controlled, “case studies” should be called “case reports”.
- p.14, Table 5 - In the third row, please correct “test up” to “tested up”
- p.15, Table 6 - Were any effects observed at the low dose in the study described in reference 5?
- p.17, Table 7 - *Salmonella typhimurium* (second row) needs to be italicized. The statement: “Not genotoxic to micronuclei in the bone marrow” does not make sense. Counting the number of micronuclei that develop is the endpoint of the assay. Did Betaine cause an increase in the number of micronuclei in the bone marrow of mice?
- p.18, Table 8 - In the first row the meaning of “16% in solids solution” does not make sense.
- p.18, Table 8 - It is not appropriate to state that a clinical study was done using OECD Guideline 404 as this guideline is for animal not human studies. Perhaps it was done in a manner similar to OECD 404?
- p.18, Table 8 - Perhaps submissions to ECHA required checking box as to whether or not a study complies to Good Laboratory Practices. Clinical studies are run according to Good Clinical Practices (see the FDA web page at <http://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/default.htm> for more information) not Good Laboratory Practices. Therefore, in the descriptions of the human studies, please deleted the statements about GLP compliance.
- p.20, Table 20 - The statement about GLP compliance needs to be deleted from the human study (reference 5) in Table 20.