Safety Assessment of Alkyl Phosphates as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	August 18, 2014
Panel Meeting Date:	September 8-9, 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.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Monice M. Fiume, Assistant Director/Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Assistant Director/Senior Scientific Analyst
Date: August 18, 2014
Subject: Safety Assessment of Alkyl Phosphates as Used in Cosmetics

Enclosed is the Draft Final Report on the Safety Assessment of Alkyl Phosphates as Used in Cosmetics. (It is identified as *alkpht092014rep_final for posting* in the pdf document.) At the June meeting, the Panel issued a Tentative Report with the conclusion that these 28 ingredients are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

Prior to the June meeting, industry submitted a guinea pig maximization study of dimyristyl phosphate that was in French. Subsequently, an English summary has been submitted. The information from that summary is now included in the safety assessment (*alkpht092014data*); 75% dimyristyl phosphate was not an irritant or sensitizer in guinea pigs.

A few issues formed the basis for the Discussion of this report. First, the Panel included the phrase "when formulated to be non-irritating" in the conclusion because test data indicated that there was some potential for ocular irritation, and potassium cetyl phosphate is used at up to 8.3% in mascara products. Additionally, some of the alkyl phosphates were irritating to the skin in animal tests; however, these studies were conducted with concentrations that were much greater than the concentrations reported to be used in cosmetics.

The Panel also noted that there were no impurities data. Based on the method of manufacture and the absence of adverse effects in repeat oral toxicity studies, the Panel was not concerned about the absence of impurities data.

Lastly, the Panel commented that, although there were no safety-test data available specifically for the triesters, these ingredients are not expected to penetrate the skin. Therefore, the Panel determined that it was appropriate to include the triesters among the ingredients in this safety assessment.

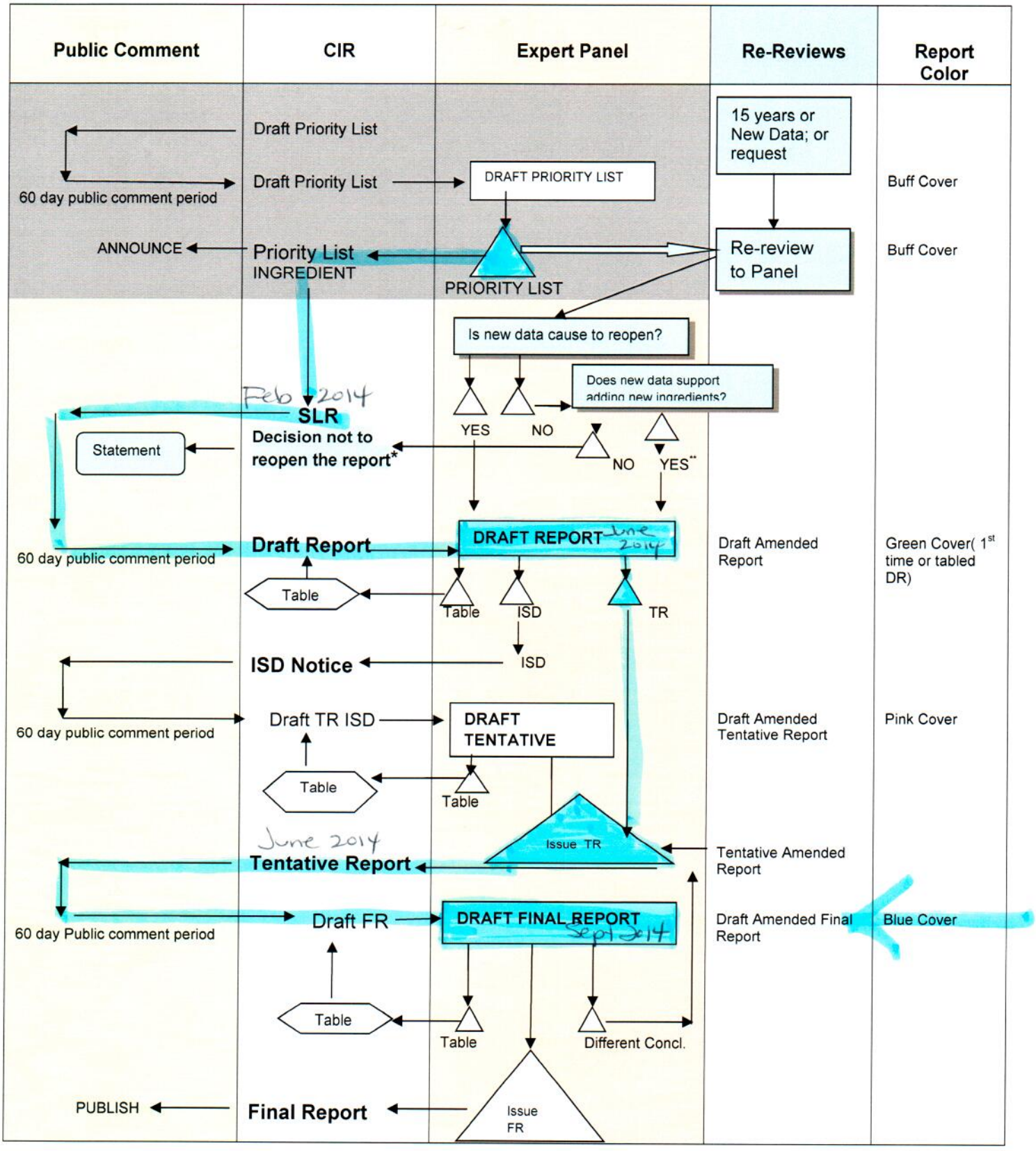
Comments on the draft (*alkpht092014pcpc_1*) and tentative reports (*alkpht092014pcpc_1*) were received from the Council and have been addressed.

The Panel should be prepared to issue a Final Report.

SAFETY ASSESSMENT FLOW CHART

Alkyl Phosphates

Sept 2014



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

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Scientific Literature Review: February 18, 2014

Concentration of use data were received and included in the SLR.

Draft Report: June 9-10, 2014

The following unpublished data submissions were received after the SLR was issued:

1. Personal Care Products Council. 2014. Memo dated February 25. Memo regarding REACH data on C20-22 Alkyl Phosphate.
2. Colonial Chemical, Inc. 2014. Safety Profile of Alkyl Phosphate Products; Council memo dated April 21, 2014.
    a. Appendix 1. Consumer Product Testing Company. 2014. Final Report. HET CAM Cola®Fax CPE-K (i.e., potassium cetyl phosphate), 3% solution.
    b. Appendix 2. Consumer Product Testing Company. 2014. Final Report. HET CAM Cola®Fax PME (i.e., potassium lauryl phosphate), 10% solution.
3. Safety studies dicetyl phosphate; Council memo dated April 14, 2014.
    a. Hazleton – IFT. 1988. Test to evaluate the cutaneous primary irritation and corrosivity, the rabbit: Dicetyl Phosphate.
    b. Hazleton – IFT. 1988. Test to evaluate acute toxicity using a single cutaneous administration (limit test), in the rat: Dicetyl Phosphate.
    c. Hazleton – IFT. 1988. Test to evaluate acute toxicity using a single oral administration (limit test), in the mouse: Dicetyl Phosphate.
    d. Hazleton – IFT. 1988. Test to evaluate acute toxicity using a single oral administration (limit test), in the rat: Dicetyl Phosphate.
    e. Hazleton – IFT. 1988. Test to evaluate acute ocular irritation and reversibility, in the rabbit: Dicetyl Phosphate.
    f. Hazleton – IFT. 1988. Test to evaluate sensitizing potential in the guinea pig: Dicetyl Phosphate
4. TKL Research, Inc. 2004. Human repeated insult patch test (leave-on hair cream containing 1.0% Dicetyl Phosphate). (Council memo dated February 27, 2014.)

Comments on the SLR also were received from the Council.

The Panel issued a Tentative Report , concluding that the 28 alkyl phosphates are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

Final Report: September 8-9, 2014

An English summary of the guinea pig maximization test of dimyristyl phosphate was received. The original study, in French, was submitted to CIR prior to the June meeting.

Comments on the draft and tentative reports were received from the Council and addressed.

Alkyl Phosphates* – Sept 2014 – Monice Fiume																	
	Reported Use	Method of Mfg	Toxicokinetics	Dermal Penetration	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhal.	Animal Tox – Rptd Dose, Derm	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhal	Repro/Dev Tox	Genotox	Carciniogenicity	Photocard	Dermal Irr/Sens	Phototoxicity	Ocular Irritation
Potassium Cetyl Phosphate	X	general info available for alkyl phosphates				X	X					X			X		X
Potassium C9-15 Alkyl Phosphate	X					X			X		X						
Potassium C11-15 Alkyl Phosphate																	
Potassium C12-13 Alkyl Phosphate	X																
Potassium C12-14 Alkyl Phosphate																	
Potassium Lauryl Phosphate	X		X			X			X			X			X		X
C8-10 Alkyl Ethyl Phosphate																	
C9-15 Alkyl Phosphate	X																
C20-22 Alkyl Phosphate	X				X	X			X		X	X			X		X
Castor Oil Phosphate	X																
Cetearyl Phosphate																	
Cetyl Phosphate	X					X						X			X		
Disodium Lauryl Phosphate																	
Disodium Oleyl Phosphate																	
Lauryl Phosphate	X														X		
Myristyl Phosphate									X								
Octyldecyl Phosphate																	
Oleyl Ethyl Phosphate																	
Oleyl Phosphate					X	X			X		X	X			X		X
Sodium Lauryl Phosphate									X		X						
Stearyl Phosphate	X																
Dicetyl Phosphate	X				X	X									X		X
Dimyristyl Phosphate					X	X									X		X
Dioleyl Phosphate	X																
Tricetyl Phosphate																	
Trilauryl Phosphate																	
Trioleyl Phosphate	X																
Tristearyl Phosphate																	

*"X" indicates that data were available in a category for the ingredient

Alkyl Phosphates

	INCI Dictionary	FDA VCRP (2013)	Conc of Use data	CFR	GRAS/DFA/ IFA/EAFUS	EU	REACH	Merck	OTC	HPV LIST	IUCLID/SIDS	IARC	NTP	JECFA	USP/NF	ChemPortal	PubMed Search	SciFinder Search	Google Search	Chem Spider	NTIS
Potassium Cetyl Phosphate 90506-45-9 (generic); 17026-85-6; 19035-79-1; 84861-79-0	X	375	X	---	---	X	X	---	---	---	---	---	---	---		ACToR; ESIS; ECHA				X	---
Potassium C9-15 Alkyl Phosphate 190454-07-0	X	---	X	---	---	X	---	---	---	---	---	---	---	---		---				---	---
Potassium C11-15 Alkyl Phosphate ***96416-89-6?? (SciFndr)***	X	---	NR	---	---	X	---	---	---	---	---	---	---	---		---				---	---
Potassium C12-13 Alkyl Phosphate ***85252-00-2?? (SciFndr)***	X	2	X	---	---	X	---	---	---	---	---	---	---	---		---				---	---
Potassium C12-14 Alkyl Phosphate	X	---	NR	---	---	X	---	---	---	---	---	---	---	---		---				---	---
Potassium Lauryl Phosphate 39322-78-6	X	4	NR	IFA - 21CFR177.1632		X	X	---	---	---		---	---	---		ACToR; ECHA; ESIS; EPA SRS				X	---
C8-10 Alkyl Ethyl Phosphate 68412-60-2	X	---	NR	---		X	---			---	---					ACToR				---	
C9-15 Alkyl Phosphate 190454-07-0	X	12	X	---		X	---			---	---					---	905	1693		---	
C20-22 Alkyl Phosphate	X	12	X	---		X	---			---	---					---				---	
Castor Oil Phosphate	X	2	NR	---		X	---			---	---					---				---	
Cetearyl Phosphate 90506-73-3	X	---	NR	---		X	---			---	---					ACToR; ESIS				---	
Cetyl Phosphate 3539-43-3	X	89	X	---		X	---			---	---					ACToR				X	
Disodium Lauryl Phosphate 7423-32-7	X	---	NR			X	---			---	---					---				---	
Disodium Oleyl Phosphate	X	---	NR				---			---	---					---				---	
Lauryl Phosphate 12751-23-4	X	3	X	---		X	---			---	---					ACToR; ESIS				---	
Myristyl Phosphate 10054-29-2	X	---	NR			X	---			---	---					ACToR				---	
Octyldecyl Phosphate 97553-81-6	X	---	NR	---		X	---			---	---					ACToR				---	
Oleyl Ethyl Phosphate 10483-96-2	X	---	NR	---		X	---			---	---					---				---	
Oleyl Phosphate 37310-83-1	X	---	NR	---		X	X			---	---					ACToR; SRS; ESIS				X	
Sodium Lauryl Phosphate	X	---	NR	---		X	---			---	---					---				---	
Stearyl Phosphate 2958-09-0	X	1	NR	---		X	---			---	---					ACToR				X	

	INCI Dictionary	FDA VCRP (2013)	Conc of Use data	CFR	GRAS/DFA/ IFA/EAFUS	EU	REACH	Merck	OTC	HPV LIST	IUCLID/SIDS	IARC	NTP	JECFA	USP/NF	ChemPortal	PubMed Search	SciFinder Search	Google Search	Chem Spider	NTIS
Dicetyl Phosphate 2197-63-9	X TRN 107	106	not surveyed	---		X	---			---	---					ACToR				X	
Dimyristyl Phosphate 6640-03-5	X	---	not surveyed	---		X	---			---	---					ACToR				X	
Dioleyl Phosphate	X	1	not surveyed	---		X	---			---	---					ACToR				X	
Tricetyl Phosphate 56827-95-3; 68814-13-1	X	---	not surveyed	---		X	---			---	---					ACToR				X	
Trilauryl Phosphate 682-49-5	X	---	not surveyed	---		X	---			---	---					ACToR				X	
Trioleyl Phosphate 3305-68-8	X	3	not surveyed	---		X	---			---	---					ACToR				X	
Tristearyl Phosphate 4889-45-6	X	---	not surveyed	IFA – 21CFR176.210		X	---			---	---					ACToR				X	

PubMed Search (1/17/13)

(Potassium AND Cetyl AND Phosphate) OR (Potassium AND Alkyl AND Phosphate) OR (Potassium AND Lauryl AND Phosphate) OR (Alkyl AND Ethyl AND Phosphate) OR (C9-15 AND Alkyl AND Phosphate) OR (C20-22 AND Alkyl AND Phosphate) OR (Castor AND Oil AND Phosphate) OR (Cetearyl AND Phosphate) OR (Cetyl AND Phosphate) OR (Disodium AND Lauryl AND Phosphate) OR (Disodium AND Oleyl AND Phosphate) OR (Lauryl AND Phosphate) OR (Myristyl AND Phosphate) OR (Octyldecyl AND Phosphate) OR (Oleyl AND Ethyl AND Phosphate) OR (Oleyl AND Phosphate) OR (Sodium AND Lauryl AND Phosphate) OR (Stearyl AND Phosphate) OR (Dicetyl AND Phosphate) OR (Dimyristyl AND Phosphate) OR (Dioleyl AND Phosphate) OR (Tricetyl AND Phosphate) OR (Trilauryl AND Phosphate) OR (Trioleyl AND Phosphate) OR (Tristearyl AND Phosphate) – 905 hits

SciFinder Search (1/21/14)

all CAS No. or terms; refined – 1693 hits
toxicity of alkyl phosphates (refined by document type) – 172 hits
dermal effects of alkyl phosphates (refined by document type) – 27 hits

EU

No restrictions; no SCCS opinion

REACH

Potassium Cetyl Phosphate – as Reaction product of phosphorus pentoxide and C16-18 (even-numbered) alcohol, neutralized with potassium hydroxide (1/13/14; searched using CAS No. 90506-45-9)

- Registrant/Suppler: Schill & Seilacher Chemie GmbH
- Home page: http://apps.echa.europa.eu/registered/data/dossiers/DISS-e5a0779b-8b9b-00b9-e044-00144f67d031/DISS-e5a0779b-8b9b-00b9-e044-00144f67d031_DISS-e5a0779b-8b9b-00b9-e044-00144f67d031.html

Potassium Lauryl Phosphate – as Phosphoric acid dodecyl ester, potassium salt (2/10/14 – searched using CAS No. 39322-78-6

- Registrant/Supplier: Clariant Produkte (Deutschland) GmbH
- Home page: http://apps.echa.europa.eu/registered/data/dossiers/DISS-db9c132f-a42a-2d31-e044-00144f67d031/DISS-db9c132f-a42a-2d31-e044-00144f67d031_DISS-db9c132f-a42a-2d31-e044-00144f67d031.html

Oleyl Phosphate – as 9-Octadecen-1-ol, (Z)-, phosphate; IUPAC name: Reaction product of oleyl alcohol with polyphosphoric acid (1/13/14; searched using CAS No. 37310-83-1; 1-24-14)

- Registrant/Supplier: Chemetall GmbH
- Home page: http://apps.echa.europa.eu/registered/data/dossiers/DISS-e1a0ab01-dba1-2fde-e044-00144f67d031/DISS-e1a0ab01-dba1-2fde-e044-00144f67d031_DISS-e1a0ab01-dba1-2fde-e044-00144f67d031.html
-

ChemSpider

- *Potassium Cetyl Phosphate* - http://www.chemspider.com/Chemical-Structure.10645292.html (1/3/14)
  - check http://www.chemspider.com/Chemical-Structure.79305.html
- *Potassium Lauryl Phosphate* - http://www.chemspider.com/Chemical-Structure.8015171.html (1/3/14)
  - check http://www.chemspider.com/Chemical-Structure.21229848.html

ALKYL PHOSPHATES - Full Panel - June 10, 2014

So moving on to the next ingredient, Dr. Marks on alkyl phosphates.

DR. MARKS: So this is the first review of these cosmetic ingredients and our team felt that we could issue a tentative report with, safe when formulated to be non-irritating, so that's a move, or a motion.

DR. BELSITO: We would second that.

DR. BERGFELD: There's a motion that's been second, to move it, a level of safety when non-irritating. Any other comments? Any comments for the discussion?

DR. BELSITO: Yeah, we didn't have impurities, but we do have negative repeat oral studies and that would need to go into our discussion as to why we were not concerned about our lack of information on impurities on these products.

DR. BERGFELD: Anything else? Any other boiler plates that need to go in? Okay. I'm going to -- I don't think I called the question on this one. I have to think. Anyway, I'm going to call it again. All those in favor, then, a safe when non-irritating, please raise your hand. Thank you, it's unanimous.

Belsito Team – June 9, 2014

DR. BELSITO: Anything else? So then, if not, alkyl phosphates. So, this is the first time we're seeing this report and there was a Wave 2 data on dermal irritation, French study that was waiting to be translated but the baseline line is of that study is it was OECD. They did 15 albino guinea pigs. They did forensagavent and they challenged up to 75 percent, and it was negative. That's the French one that hasn't been translated. So, you had 75 percent non-sensitizing.

And then we have two -- we have an eye study on Mexoryl and an oral tox study on Mexoryl plus what was in the original report. So, let me save Rosemary here and find alkyl phosphates. So, the only comment that I made was that while the myristyl didn't seem to irritate, there was some data in this report suggesting that some of these alkyl phosphates could be irritating, so I thought we could go with a "safe as used when formulated not to be irritating", so I'll open that suggestion up for comments team.

DR. LIEBLER: That's what I had as well.

DR. SNYDER: I wanted to ask Dan if there's anything that I'm -- or Kurt -- if anything in the method manufacture that would make us suspicious about potential impurities.

DR. BELSITO: Well, I have that question about impurities.

DR. SNYDER: There's no impurity data and I -- so they use an alcohol with a phosphorus trichloride and carbon tetrachloride, so I didn't know if there was any need to have impurity data, because we don't have any.

DR. BELSITO: Well, we had that oral -- well, I guess we don't have an oral study for every one.

DR. SNYDER: The myristyl phosphate, we have an oral rat study in Wave 2.

DR. BELSITO: Um-hmm.

DR. LIEBLER: Based on the method of manufacture I'm not particularly concerned about impurities. I mean the leftovers in the reaction will be phosphoric acid or hydrogen chloride or salt in those -- sodium chloride, pretty innocuous stuff.

DR. BELSITO: Yeah, and we have multiple repeated dose oral studies in animals on several of them, like potassium C9-15, alcohol phosphate, potassium (inaudible) phosphate, and they were all pretty clean.

DR. LIEBLER: I would suggest that just on the chemistry page, just the structure is shown, that you actually re-do the structure with a representation of the fatty aceyl substituents to give a better representation of what the molecule's like because this just looks like it's, you know, phospho-R. You know, it looks -- you just started showing the polar piece so.

DR. BELSITO: Any other comments?

MS. FIUME: Do you have specific items for the discussion that I can build on?

DR. BELSITO: I didn't flag anything.

SPEAKER: You could do the impurities or lack of and --

DR. BELSITO: Okay, lack of data for impurities, sure. And the fact that we had repeat oral tox studies on several of these that were clean, and Dan can make his comments again about what it would break down to or what would be left residual.

DR. LIEBLER: Right, (inaudible) got that, right?

DR. BERGFELD: You could also do the eye irritation and the skin studies and for the reason for your concern about compounding or formulating to be non- irritating.

DR. BELSITO: Okay.

DR. LIEBLER: Yeah, the irritation was with undiluted or high concentrations that exceeded use levels.

DR. BELSITO: I don't -- did it exceed use levels? Again, I've reviewed these, like, over a month ago, so this is just a note to myself.

DR. LIEBLER: Well, that's what I wrote to myself.

DR. BELSITO: Okay. So then we don't have to put when formulated not to be irritating?

DR. LIEBLER: Well, I also put when formulated to be non-irritating, and I'm trying to remember why I did that.

DR. BELSITO: Oh, well, let's take a look.

DR. LIEBLER: So, top-use concentrations -- where were we with this again?

MS. FIUME: 8.3 in a mascara.

DR. LIEBLER: 8.3?

MS. FIUME: And then 4.2 in leave-on dermal.

DR. LIEBLER: Okay.

MS. FIUME: Irritation was at 10.

DR. SNYDER: It's irritating to the rat at 77 percent paste which is pretty high.

DR. BELSITO: So Table 10 is where they have the animal data, and then let me see if there's anything else before that rat irritation.

MS. FIUME: There was some eye but it was at 10%, and then at 3% it wasn't. It was a 10 percent solution tested as a 50 percent dilution in a HET-CAM. There was ocular irritation potential and if you use that 8 point something in a mascara, so it doesn't -- how should that be addressed in the discussion?

DR. BELSITO: When formulated not to be irritating. Table 10 is where that data was. Okay, so oleyl phosphate (inaudible) --

DR. LIEBLER: So, we're looking for anything that's irritating at 5 percent or less, right?

DR. BELSITO: Yeah.

DR. LIEBLER: I'm not seeing it.

DR. BELSITO: Potassium lauryl sulfite, paste in.9 percent, concentration not specified, highly irritating.

DR. LIEBLER: Well, paste implies highly concentrated.

DR. BELSITO: Oleyl phosphate undiluted, yeah. Oleyl phosphate, 10 percent, 25 percent, 50 percent, 75 percent. Preliminary irritation study for LLNA, significant irritation at 10 percent, and we're looking at 8 percent top leave-on.

MS. FIUME: Top dermal leave on was, I believe, four.

DR. BELSITO: Four in a mascara.

MS. FIUME: No, the mascara was 8.3, and there was ocular irritation study, and then 4.2 in a dermal leave-on for tri-oleyl phosphate. And then the highest rinse-off was 8.7 percent.

DR. BELSITO: I mean --

DR. BERGFELD: I think you're okay with non- irritating.

DR. BELSITO: Yeah, I mean we have some concerns and industry should never manufacture anything that's a day-to-day irritate anyway, so I think that just covers our base, and we can point out that any issue with the mascara or the ocular irritation in the discussion and the fact there are some reports that concentrations at 10 percent -- I mean, so basically for oleyl phosphate we know that up to 5 percent in that LLNA study didn't seem to be irritating. We know that 10 percent was irritating. We don't know where it lies in-between, and it could be used in a mascara up to 8, right? So, it could be irritating not only to the eye but to the eyelid if it were used, so when formulated, safe when formulated not to be irritating, and that's really the only concern I had with these. Can deal with the lack of impurities by the repeated oral studies. New comment annotations. Okay, any other comments? No? Okay.

DR. HILL: Alkyl phosphates.

DR. MARKS: Alkyl phosphates. And, Ron, do you want to comment? You jumped on that.

DR. HILL: No. I'm not -- that wasn't mine.

DR. MARKS: So, this is the first review; there are 28 ingredients, what are the needs, are the ingredients okay? So let's first go to the ingredients like we normally do, and is there anything that stands out in the ingredients that shouldn't be included? And I normally go to the table which has the -- this is on page 6.

DR. HILL: I always have read across issues but that was related to throwing out.

DR. MARKS: So all these look like they should be included. Yeah?

DR. SHANK: No -- Yeah. No.

DR. MARKS: No?

DR. SHANK: I see the triesters should be separated out, they have a different function.

DR. MARKS: By function?

DR. SHANK: Yes.

DR. MARKS: Not by chemical?

DR. SHANK: No.

DR. MARKS: So you're talking about tricetyl, trilauryl, Trioleyl --

DR. SHANK: Yes.

DR. MARKS: -- and tristearyl. So all those, delete Where is Bart? So a different function --

DR. SHANK: They have a different function as opposed to the others.

DR. HELDRETH: And I want to remind that the functions are not validated, but it is vetted out against these functions. Someone can submit a request for an INCI name and say it has this function, and that's what gets recorded. So I'd be worried of basing conclusions on functions. Since some things appear to just (inaudible) but could actually function in another way. There's another function in the dictionary that's called skin conditioning agent miscellaneous, which means absolutely nothing. So I would be careful basing the conclusion on the function.

DR. SHANK: I wasn't basing the conclusions --

DR. HELDRETH: Okay.

DR. SHANK: -- just the grouping.

DR. HELDRETH: Likewise.

DR. MARKS: That's why I'm calling on you, Bart.

DR. HELDRETH: And I made it back.

DR. MARKS: So, what was it about the function that --

DR. SHANK: That we founded.

DR. MARKS: Good. Okay. Let's see what I have.

DR. SLAGA: Well the triethyl's function is plasticized, rather than (inaudible) --

SPEAKER: Like what you said again --

MS. FIUME: It's PDF, page 11.

DR. SHANK: Thank you.

DR. MARKS: Pardon me?

MS. FIUME: PDF, page 11, the introduction. It's the first paragraph under the listing of ingredients.

DR. SLAGA: We really don't have any data on any of the triesters anyway.

DR. SHANK: Correct. Only on one of them.

DR. MARKS: So that's what you saw. So with it being a plasticizer, would it change the conclusion if you say formulated, you know, in the (inaudible) data; unless you have other toxicological (phonetic) concerns? Because I think that's what I remember as a possible conclusion.

DR. SLAGA: Well some of them are irritants of high concentration.

DR. MARKS: Yeah. That's why -- but I was thinking with Ron.

DR. SLAGA: None of them are genotoxic --

DR. MARKS: Right.

DR. SLAGA: -- what data we have. It's all from in the summary.

DR. MARKS: And then the other thing -- so I'm going to let Ron -- can have a look -- at least on page 29, let me look at that. I have a question. Is the cetyl phosphate at the top of table 10? I assume that's potassium cetyl phosphate, because I don't know, there's cetyl phosphate too, I'm sorry.

MS. FIUME: There is cetyl phosphate.

DR. MARKS: Yeah. So that's cetyl phosphate. Okay. It's not a sensitizer. Okay. So, Ron Hill, Tom, what do you think about the triesters?

DR. SLAGA: Well, I didn't have any problem with them. I guess I didn't really look, I thought that was much of a change and function. They are obvious, you know, be much larger in their potential to get on the skin, so it's going to be very slim, at best.

DR. MARKS: Okay.

DR. SHANK: We didn't have no -- we have no data at all relate to the triesters. It's all based on the (inaudible), if you will.

DR. SLAGA: If you go make them more -- aren't the triesters more lipophilic?

DR. HILL: Sure.

DR. SHANK: So wouldn't they tend to irritate the skin --

DR. HILL: Much more than lipophilic --

DR. SHANK: -- a little better?

DR. HILL: They may have, probably only if the change is pretty small.

DR. SLAGA: But we have no data --

DR. HILL: Yeah. But yes.

DR. SHANK: We don't have any data on that.

DR. MARKS: So in that case we wouldn't eliminate then, we would just say, insufficient data notice for the triesters.

DR. SLAGA: Can we say that approach. That, to me, would be -- we may get something, you know.

DR. SHANK: Okay. That would be all right.

DR. MARKS: So let me leave two note tox for these. So let me go down here, so yeah, so (inaudible) for triesters, don't we want the absorption data for that?

DR. SHANK: Yes.

MS. FIUME: Is it accompanied with (inaudible) and those (inaudible) too slow at all?

DR. SHANK: It was calculated in what, RA?

MS. FIUME: For tricetyl, the calculated LogP is 22.17, and the molecular weight is 771. Trilauryl is molecular weight, 603, with a calculated LogP of 17.02.

DR. MARKS: Okay.

MS. FIUME: Trioleyl is molecular weight 849, calculated LogP of 25.03. And on the tristearyl is molecular weight 855. Let me go back and check this one, I have the calculated LogP as 225.2 --

DR. HILL: That's sounds about right.

MS. FIUME: I think this is --

SPEAKER: No, that sounds --

MS. FIUME: That's right? Okay.

SPEAKER: You know, calculations get fuzzy at that point anyway, but that sounds about right.

MS. FIUME: Okay. So 225.

DR. MARKS: So it doesn't sound like we really need that then, do you?

DR. HILL: The thing is with LogPs as high as 30 can get into the skin, they aren't going to come out of the skin that way at any significant rate. All they have to do is raise the blood flow but -- And so what? In this case I guess.

DR. SHANK: So then you'd have to say in the discussion that the (inaudible) fields of the triester phosphates will not penetrate into circulation, and therefore the whole group is safe if formulated to be non- irritating.

DR. MARKS: Does that sound acceptable.

DR. SLAGA: Okay.

DR. MARKS: Okay.

DR. SHANK: I thought I'd make the chemist happy with my proposal after the sulfate story, but it's okay --

DR. HILL: I can definitely see your point of view, and I'm surprised I'm not on the same bandwagon, beating that same drum, but --

DR. MARKS: Okay. So tomorrow I'm going to -- now, do we need impurities? That was missing on page 12, and before we didn't -- is that correct? Or at least that I overlooked, and I don't remember seeing impurities in Wave 2.

MS. FIUME: No. The only thing I did find and may (inaudible) is there's very little impurities, and it was just the amount of C20, that's 22 alkyl phosphates contains less than 1 percent phosphoric acid, other than that, we don't have any impurities data.

DR. MARKS: Do we need anything?

DR. SHANK: No.

DR. MARKS: No.

DR. HILL: I don't think so either.

DR. MARKS: Okay. So let's see, who is doing this one tomorrow? I am. I am going to move that we issue a tentative report for the conclusion, safe when formulated to be non-irritating. And then if we want to go -- Ron Shank, do you want to -- when we ask for discussion points, although that will be in the document when we see the tentative the next round; and it's obviously (inaudible) -- concerning absorptions.

DR. SHANK: That's fine.

DR. MARKS: Okay. Any other comments about the alkyl phosphates?

DR. HILL: You have one question pertaining to the cross (inaudible), if I can find it.

SPEAKER: Page 11.

DR. HILL: It's more to the question of why is that statement in here, so hang on, I have the PDF -- PDF page 11. You have phosphoric acid 2-ethylhexyl ester, that's not one of the ingredients, right?

MS. FIUME: I'm sorry?

DR. HILL: Phosphoric acid 2-ethylhexyl ester, that's not one of the ingredients, correct?

MS. FIUME: Hmm?

DR. HILL: You're using it somewhere in here for read across, I think. I have to search that ethylhexyl because --

SPEAKER: It's not in the --

MS. FIUME: The ECHA data use that as read across for potassium lauryl phosphate, and that is the rationale that they gave.

DR. MARKS: Okay. I want to make sure it wasn't the other direction, because there were specific issues with two ethylhexanoates --

MS. FIUME: Yes.

DR. MARKS: -- but it's the other way around?

MS. FIUME: It's the other way around.

DR. MARKS: Okay. Cool. We are good.

MS. FIUME: Yeah. It was being used as read across for potassium lauryl phosphate.

DR. HILL: I think I flagged this. At the time I flagged it, it was early, and my reading of this was to makes sure that this wasn't a (inaudible) of the ingredient, per se.

MS. FIUME: It's not.

DR. MARKS: Okay.

DR. HILL: Or at least one of the ones on our list. Yeah?

MS. FIUME: Mm-hmm.

DR. HILL: Good. Okay.

Safety Assessment of Alkyl Phosphates as Used in Cosmetics

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The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Monice M. Fiume, Assistant Director/Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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ABSTRACT

The Expert Panel assessed the safety of 28 alkyl phosphates and concluded that these ingredients are safe in the current practices of use and concentration when formulated to be non-irritating. The ingredients in the alkyl phosphate family share a common phosphate core structure, and vary by the identity of the alkyl chains attached therein. Most of the alkyl phosphates function as surfactants in cosmetic ingredients; however the triesters function as plasticizers rather than surfactants. The Panel reviewed the available animal and clinical data to determine the safety of these ingredients.

INTRODUCTION

This report is a safety assessment of the following 28 alkyl phosphates as used in cosmetic formulations:

Potassium Cetyl Phosphate
Potassium C9-15 Alkyl Phosphate
Potassium C11-15 Alkyl Phosphate
Potassium C12-13 Alkyl Phosphate
Potassium C12-14 Alkyl Phosphate
Potassium Lauryl Phosphate
C8-10 Alkyl Ethyl Phosphate
C9-15 Alkyl Phosphate
C20-22 Alkyl Phosphate
Castor Oil Phosphate
Cetearyl Phosphate
Cetyl Phosphate
Disodium Lauryl Phosphate
Disodium Oleyl Phosphate
Lauryl Phosphate
Myristyl Phosphate
Octyldecyl Phosphate
Oleyl Ethyl Phosphate
Oleyl Phosphate
Sodium Lauryl Phosphate
Stearyl Phosphate
Dicetyl Phosphate
Dimyristyl Phosphate
Dioleyl Phosphate
Tricetyl Phosphate
Trilauryl Phosphate
Trioleyl Phosphate
Tristearyl Phosphate

The ingredients in the alkyl phosphate family share a common phosphate core structure, and vary by the identity of the alkyl chains (ranging from 8 to 22 carbons in length) attached. Most of the alkyl phosphates are reported to function as surfactants in cosmetic ingredients; however the triesters function as plasticizers rather than surfactants (Table 1).[1]

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[2] The ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited. In several instances, structural analogs were used as supporting substances to provide read-across. Specifically *phosphoric acid, C16-18 alkyl esters, potassium salts* is used as read-across for potassium cetyl phosphate. Although not identical, the distribution of chain-lengths for these two ingredients will have a great deal of overlap, e.g., both will contain 15- and 16-carbon chain lengths. *1-Octadecanol, phosphate, potassium salt* also is relevant to the safety of potassium cetyl phosphate because potassium cetyl phosphate is a distribution of chain-lengths (a mixture) attached to phosphate, with a mean peak at 16-carbons in length, and *1-octadecanol, phosphate, potassium salt* is a distribution of chain-lengths attached to phosphate, with a mean peak at 18-carbons in length. Both include some longer and some shorter fatty acid residues (e.g., 14- and 18-carbon chains and 16- and 20-carbon chains, respectively). Accordingly, some read-across may be accessible between these two ingredients, as their mean chain-lengths only differ by two carbons and there are at least some literally identical chain-lengths shared by the two ingredients (in light of the complete length-distribution of each ingredient). Additionally, *phosphoric acid, 2-ethylhexyl ester* was justified as read-across for potassium lauryl phosphate because both are members of the phosphoric acid, acyl ester family, and the characteristic and functional active center of both substances is the ester binding between the alcoholic compound and phosphate. When providing information on a structural analog, the name of that analog is italicized to indicate read-across is being employed.

CHEMISTRY

Definition and Structure

Alkyl phosphates are the organic esters of ortho-phosphoric acid. These ingredients are mixtures of esters and salts wherein a phosphate may have one to three alkylations and one to two potassium or sodium cations (Figures 1 and 2; Table 1).

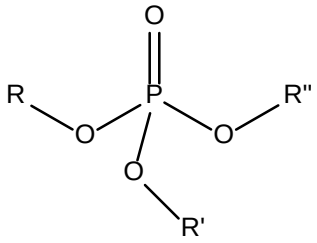


Figure 1. Alkyl Phosphates
R, R', and R" may be alkyl groupings (e.g., cetyl), hydrogen, or electron pairs with potassium or sodium cations.

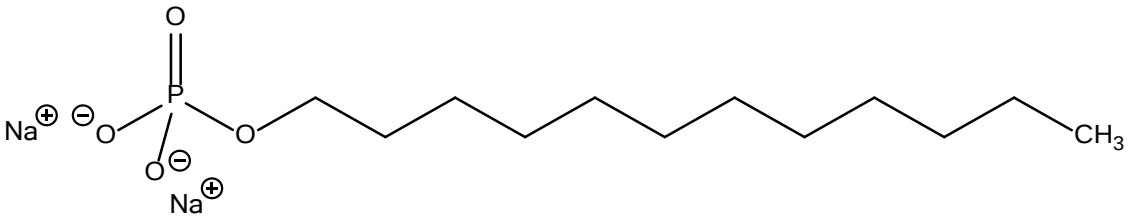


Figure 2. Disodium Lauryl Phosphate, for example, has sodium cations for R and R', and a lauryl chain for R"

These ingredients share some similarities, in structures and properties, with the natural phosphatides, lecithin and cephalin.[3] But these ingredients differ by the lack of core glyceryl structures and the resultant lack of susceptibility to enzymatic degradation. With solubility across polar and non-polar solvents, it is not surprising that these ingredients are commonly used as surfactants, wetting agents, and emulsifiers in cosmetic applications.

Chemical and Physical Properties

The alkyl phosphates can be liquids or solids (Table 2). They have solubility across polar and non-polar solvents.

Methods of Manufacture

Alkyl phosphates can be prepared by reactions of fatty alcohol with polyphosphoric acid to yield the corresponding alkyl phosphates.[4] Dialkyl phosphates can be prepared by a stepwise procedure via the monoalkyl phosphate from pyrophosphoric acid using tetramethylammonium hydroxide as a base.[5] They also can be prepared by the reaction of two equivalents of alcohol with phosphorus oxychloride followed by hydrolysis of the intermediate phosphoroxychloride. Dialkyl phosphates also have been synthesized by the reaction of the appropriate alcohol with phosphorus trichloride followed by treatment with pyridine and carbon tetrachloride, which provides the corresponding trichloromethyl ester. Reaction of the triethylamine salt of acetic acid, followed by hydrolysis of the mixed anhydride that formed, yields the dialkyl phosphate.

C20-22 alkyl phosphate is obtained from the reaction of alcohols, C20-22 with phosphoric anhydride.[6]

Constituents/Impurities

C20-22 alkyl phosphate contains <1% phosphoric acid.[6] No other published constituent data were found, and no unpublished data were submitted.

USE

Cosmetic

Most of the alkyl phosphates are reported to function as surfactants in cosmetic ingredients; however the triesters function as plasticizers rather than surfactants (Table 1).[1] Surfactants, or surface-active agents, have the ability to lower the surface tension of water or to reduce the interfacial tension between two immiscible substances. Plasticizers are materials that soften synthetic polymers.

The FDA collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). VCRP data obtained from the FDA in 2014,[7] and data received in 2013-2014 in response to surveys of the maximum reported use concentration by category that were conducted by the Personal Care Products Council (Council),[8,9] indicate that 13 of the 28 ingredients included in this safety assessment are currently used in cosmetic formulations.

According to the VCRP data, potassium cetyl phosphate is reported to be used in 375 formulations, the majority of which are leave-on formulations, dicetyl phosphate is reported to be used in 109 formulations, and cetyl phosphate in 94 formulations (Table 3).[7] All other in-use ingredients are reported to be used in less than 15 formulations. The results of the concentration of use surveys conducted by the Council indicate potassium cetyl phosphate also has the highest concentration of use in a leave-on formulation; it is used at up to 8.3% in mascara products.[8] The highest concentration of use reported for products resulting in leave-on dermal exposure is 4.2% trioleyl phosphate in "other" make-up preparations;[9] lauryl phosphate is used at 8.7% in a skin cleaning product, which is most likely a rinse-off formulation.[8] The ingredients not reported to be used, according to VCRP data and the Council survey, are listed in Table 4.

A few of the ingredients are used in products that could be incidentally ingested (e.g., up to 1% trioleyl phosphate in lipsticks) or used near the eye or mucous membranes (e.g., up to 8.3% potassium cetyl phosphate in mascara formulations). One ingredient, C20-22 alkyl phosphate, is reported to be used at 1.1% in a baby product. Additionally, according to the VCRP, dicetyl phosphate is used in a hair spray, which is a product that can be incidentally inhaled; however, the Council survey did not report a concentration of use for this product type. In practice, 95 to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[10,11] 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.[12,13]

All of the alkyl phosphates named in this safety assessment are listed in the European Union inventory of cosmetic ingredients.[14]

Non-Cosmetic

Potassium lauryl phosphate can be used as an optional finish component in poly(phenyleneterephthalamide) resins, which are indirect food additives intended for repeated contact with food; the total weight of potassium lauryl phosphate is not to exceed 1% of the base polymer [21CFR177.1632]. Tristearyl phosphate is approved as an indirect food additive as a substance permitted to be used in the formulation of defoaming agents used in the manufacture of paper and paperboard [21CFR176.210].

The use of dicetyl phosphate in niosomes (nonionic surfactant-based vesicles)[15-17] and solid lipid nanoparticles[18] has been investigated. Niosomes are microscopic vesicles composed of non-ionic surface-active agent bilayers, and the intended use of these vesicles is as a drug delivery system.[16,17] Solid lipid nanoparticles are another possible dermal delivery system.[18]

TOXICOKINETICS

Oral

Potassium Lauryl Phosphate

Five male and five female F344 rats were given a single dose of 200 mg/kg bw *phosphoric acid, 2-ethylhexyl ester* in corn oil by gavage.[19] (As stated previously, information on *phosphoric acid, 2-ethylhexyl ester* is being provided as read-across for potassium lauryl phosphate. Specifically, with reference to the occurrence of esterases which take part in the mammalian phase I metabolism, it can be assumed that both phosphoric acid esters are hydrolyzed independent from the constitution of the alcoholic part. Since the ester binding is the specific target of endogenous esterases, it is justified to perform a read across between both ester-type substances in order to estimate potential metabolism.) There were no control animals, and no positive controls. Urine and feces were collected every 12 h for 72 h after dosing. Analysis of the samples via P^{31}-nuclear magnetic resonance (NMR) spectroscopy indicated the ester was completely hydrolyzed to phosphate and 2-ethylhexanol; only a phosphate peak was found in the urine samples. The conclusion of this summary report stated *phosphoric acid, 2-ethylhexyl ester* was efficiently absorbed, metabolized, and excreted quantitatively by the body, and there was no indication of accumulation; however, no details were provided.

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

Dermal, oral, and inhalation single-dose toxicity testing has been performed with some alkyl phosphates (Table 5). These ingredients are relatively non-toxic. The dermal LD_{50} in rats was >2 g/kg bw for C20-22 alkyl phosphate,[20] oleyl phosphate,[21] and for 45.45% and 80% dicetyl phosphate.[22,23] In rats, the oral LD_{50} was >2 g/kg for *1-octadecanol, phosphate, potassium salt*,[22] potassium C9-15 alkyl phosphate,[22] C20-22 alkyl phosphate,[20] oleyl phosphate,[21] and dimyristyl phosphate;[24] the oral LD_{50} of 25% potassium lauryl phosphate was 10.49 g/kg;[19] and for 10% cetyl phosphate it was >4.7 g/kg.[22] In both the mouse[25] and rat,[26] the oral LD_{50} of a 25% suspension of dicetyl phosphate was >5 g/kg. In a 4-h exposure inhalation study, the LC_{50} of 1% aq. *phosphoric acid, C16-18 alkyl esters, potassium salts* was > 200 µl/L.[22]

Repeated Dose Toxicity

Repeated dose oral toxicity studies were performed in rats for several alkyl phosphates (Table 6). In 14-day studies, potassium lauryl phosphate had a no-observable adverse effect level (NOAEL) of 600 mg/kg bw/day for both males and females, and oral administration of up to 1000 mg/kg bw/day sodium lauryl phosphate for 14 days did not result in any adverse effects;[19] no remarkable effects were observed with up to 1000 mg/kg bw/day C20-22 alkyl phosphate by gavage.[20] The no-observed effect levels (NOELs) of myristyl phosphate in a 28-day dietary study were 1564 mg/kg bw/day for males and 227 mg/kg bw/day for females, and the NOAEL was 1564 mg/kg bw/day for females.[22] Oleyl phosphate had a NOAEL of 1000 mg/kg bw/day for male and female rats in a 28-day gavage study.[21] In a 91-day gavage study, potassium C9-15 alkyl phosphate had a benchmark dose lower confidence limit of 240.3 mg/kg bw/day in males and females.[22]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Potassium C9-15 alkyl phosphate was not embryotoxic, fetotoxic, or teratogenic in rats dosed by gavage on days 6-15 of gestation; the NOELs for developmental toxicity, embryotoxicity, fetotoxicity, and teratogenicity were 361 mg/kg bw/day (active ingredient (a.i.)), and the NOEL and NOAEL for maternal toxicity were 36.1 and 361 mg/ kg bw/day (a.i.), respectively (Table 7).[22] For C20-22 alkyl phosphate, the NOELs for reproduction (mating and fertility) and neonatal toxicity, and the NOAEL for parental toxicity, were 1000 mg/kg bw/day in rats.[20] Oleyl phosphate also was not a reproductive toxicant in rats; in a gavage study, the NOAELs were 1000 mg/kg bw/day for maternal toxicity, reproductive performance in male and female rats, and development in F_1 offspring.[21] In a reproductive study with sodium lauryl phosphate in rats, the NOAEL for parental male and female animals and the NOEL for the F_1 generation was 1000 mg/kg bw/day.[19]

GENOTOXICITY

In vitro genotoxicity assays have been performed on several of the alkyl phosphates, and the results of all these assays were negative (Table 8). *1-Octadecanol, phosphate, potassium salt* was negative in an Ames test,[22] and cetyl phosphate was not genotoxic in a mammalian cell gene mutation assay.[22] Potassium lauryl phosphate,[19] C20-22 alkyl phosphate,[20] and oleyl phosphate[21] were not mutagenic in the Ames test, mammalian cell gene mutation assay, or chromosomal aberration assay.

CARCINOGENICITY

Published carcinogenicity data were not found, and no unpublished data were submitted.

IRRITATION AND SENSITIZATION

Some alkyl phosphates were not dermal irritants, whereas several were irritating but not sensitizing, in non-human studies (Table 9). C20-22 alkyl phosphate, applied neat, was not irritating to rat skin,[20] nor was it a sensitizer in a guinea pig maximization test (GPMT).[20] Undiluted *phosphoric acid, C16-18 alkyl esters, potassium salts* produced some signs of irritation in the abraded skin of rabbits.[22] Potassium lauryl phosphate was irritating to rabbit skin as a 77% paste in one study, and highly irritating to rabbit skin in another (concentration not specified); it was not a sensitizer in a GPMT.[19] Cetyl phosphate and lauryl phosphate were not sensitizers in GPMTs, but challenge concentrations of 10% and 40% cetyl phosphate and an epidermal induction concentration of 12.5% lauryl phosphate were irritating.[22] Undiluted oleyl phosphate was irritating to rat skin; concentrations up to 5% did not demonstrate a potential for sensitization in a local lymph node assay.[21] (Alternative studies with oleyl phosphate did not demonstrate a potential for skin irritation or corrosion.) Dicetyl phosphate was not irritating to rat skin as an

80% paste,[22] was not irritating to rabbit skin when prepared as a 46.5% paste in olive oil (w/w),[27] and was not a sensitizer in a GPMT.[28] Dimyristyl phosphate, applied under an occlusive patch for 4 h, was not irritating to rabbit skin,[29] nor was it an irritant or sensitizer in guinea pigs at a concentration of 75% in distilled water.[30]

C20-22 alkyl phosphate, 5% in an emulsion, was not an irritant or a sensitizer in a human repeated insult patch test (HRIPT) completed in 49 subjects.[20] In an HRIPT completed in 108 subjects, a hair cream containing 1.0% dicetyl phosphate was not a sensitizer.[31]

Case Report

Trioleyl Phosphate

A female subject with severe contact dermatitis on the eyelids was patch-tested with ingredients from the cosmetic formulation suspected of causing the reaction; the product was a lipstick that was mistaken for an eyeshadow.[22] The subject had positive reactions to three ingredients, one of which was trioleyl phosphate. The patch testing was repeated using patch test chambers secured to the back. Positive reactions were observed with 0.5% and 1% trioleyl phosphate in petrolatum on days 4 and 7, but not on day 2. The patient did not react to 1-10% cetyl phosphate in petrolatum. Negative results were reported in 20 control subjects patch tested with 1% trioleyl phosphate in petrolatum.

Ocular Irritation

Some of the alkyl phosphates are reported to be ocular irritants (Table 10). A 10% solution of potassium lauryl phosphate, tested as a 50% dilution in the hen's egg test utilizing the chorioallantoic membrane (HET-CAM), demonstrated moderate ocular irritation potential,[32] and undiluted oleyl phosphate demonstrated the potential to be corrosive and a severe ocular irritant in an *in vitro* eye corrosives and severe irritants study.[21] In rabbit eyes, potassium lauryl phosphate was an irritant,[19] C20-22 alkyl phosphate was a moderate irritant,[20] and dicetyl phosphate was slightly irritating.[33] However, a 3% potassium cetyl phosphate solution, tested as a 50% dilution in the HET-CAM, demonstrated practically no ocular irritation potential,[34] and *phosphoric acid, C16-18 alkyl esters, potassium salts*[22] and dimyristyl phosphate[35] were classified as non-irritating to rabbit eyes.

SUMMARY

This report addresses the safety of 28 alkyl phosphates as used in cosmetics. The ingredients in the alkyl phosphate family share a common phosphate core structure, and vary by the identity of the alkyl chains attached therein. In some instances, structural analogs were used as supporting substances to provide read-across. Specifically, *phosphoric acid, C16-18 alkyl esters, potassium salts* and *1-octadecanol, phosphate, potassium salt* provided read-across for potassium cetyl phosphate, and *phosphoric acid, 2-ethylhexyl ester* provided read-across for potassium lauryl phosphate.

Most of the alkyl phosphates function as surfactants in cosmetic ingredients; however the triesters function as plasticizers rather than surfactants. VCRP data obtained from the FDA in 2014, and data received in response to a survey of the maximum reported use concentration by category conducted by Council in 2013-2014, indicate that 13 of the 28 ingredients included in this safety assessment are used in cosmetic formulations. Potassium cetyl phosphate is reported to be used in 375 formulations, dicetyl phosphate in 109 formulations, and cetyl phosphate in 94 formulations. All other in-use ingredients are reported to be used in less than 15 formulations. Potassium cetyl phosphate has the highest concentration of use in a leave-on formulation, i.e., up to 8.3% in mascara products. The highest concentration of use reported for products resulting in leave-on dermal exposure is 4.2% trioleyl phosphate in "other" make-up preparations.

A single oral dose of *phosphoric acid, 2-ethylhexyl ester to F344 rats* was completely hydrolyzed to phosphate and 2-ethylhexanol. The ester was reported to be efficiently absorbed, metabolized, and excreted quantitatively by the body, and there was no indication of accumulation.

The alkyl phosphate ingredients are relatively non-toxic in single-dose studies. The dermal LD_{50} in rats was >2 g/kg bw for C20-22 alkyl phosphate, oleyl phosphate, and 45.45% and 80% dicetyl phosphate. The oral LD_{50} in rats was >2 g/kg for *1-octadecanol, phosphate, potassium salt*, potassium C9-15 alkyl phosphate, C20-22 alkyl phosphate, oleyl phosphate, and dimyristyl phosphate. The oral LD_{50} of 25% potassium lauryl phosphate was 10.49 g/kg, and for 10% cetyl phosphate it was >4.7 g/kg. In both the mouse and rat, the oral LD_{50} of a 25% suspension of dicetyl phosphate was >5 g/kg. In a 4-h inhalation study, the LC_{50} of 1% aq. *phosphoric acid, C16-18 alkyl esters, potassium salts* was > 200 µl/L.

In 14-day studies, potassium lauryl phosphate had a NOAEL of 600 mg/kg bw/day for both males and females, and oral administration of up to 1000 mg/kg bw/day sodium lauryl phosphate for 14 days did not result in any adverse effects; no remarkable effects were observed with up to 1000 mg/kg bw/day C20-22 alkyl phosphate by gavage. The NOELs of myristyl phosphate in a 28-day dietary study were 1564 mg/kg bw/day for males and 227 mg/kg bw/day for females, and the NOAEL was 1564 mg/kg bw/day for females. Oleyl phosphate had a NOAEL of 1000 mg/kg bw/day for male and female rats in a 28-day gavage study. In a 91-day gavage study, potassium C9-15 alkyl phosphate had a benchmark dose lower confidence limit of 240.3 mg/kg bw/day in males and females.

Potassium C9-15 alkyl phosphate was not embryotoxic, fetotoxic, or teratogenic in rats dosed by gavage on days 6-15 of gestation; the NOELs for developmental toxicity, embryotoxicity, fetotoxicity, and teratogenicity were 361 mg/kg bw/day (a.i.), and the NOEL and NOAEL for maternal toxicity were 36.1 and 361 mg/ kg bw/day (a.i.), respectively. For C20-22 alkyl phosphate, the NOELs for reproduction (mating and fertility) and neonatal toxicity, and the NOAEL for parental toxicity, were 1000 mg/kg bw/day in rats. Oleyl phosphate also was not a reproductive toxicant in rats; in a gavage study, the NOAELs were 1000 mg/kg bw/day for maternal toxicity, reproductive performance in male and female rats, and development in F_1 offspring. In a reproductive study in rats with sodium lauryl phosphate, the NOAEL for parental male and female animals and the NOEL for the F_1 generation was 1000 mg/kg bw/day.

1-Octadecanol, phosphate, potassium salt was negative in an Ames test, and cetyl phosphate was not genotoxic in a mammalian cell gene mutation assay. Potassium lauryl phosphate, C20-22 alkyl phosphate, and oleyl phosphate were not mutagenic in the Ames test, mammalian cell gene mutation assay, or chromosomal aberration assay.

Some alkyl phosphates were not irritating to the skin, whereas several were irritating, but not sensitizing, in non-human studies. C20-22 alkyl phosphate, applied neat, was not irritating to rat skin, nor was it a sensitizer in a GPMT. Undiluted *phosphoric acid, C16-18 alkyl esters, potassium salts* produced some signs of irritation in the abraded skin of rabbits. Potassium lauryl phosphate was irritating to rabbit skin as a 77% paste in one study, and highly irritating to rabbit skin in another (concentration not specified); it was not a sensitizer in a GPMT. Cetyl phosphate and lauryl phosphate were not sensitizers in GPMTs, but challenge concentrations of 10 and 40% cetyl phosphate and an epidermal induction concentration of 12.5% lauryl phosphate were irritating. Undiluted oleyl phosphate was irritating to rat skin; concentrations up to 5% did not demonstrate a potential for sensitization in a local lymph node assay. (Alternative studies with oleyl phosphate did not demonstrate a potential for skin irritation or corrosion.) Dicetyl phosphate was not irritating to rat skin as an 80% paste, was not irritating to rabbit skin when prepared as a 46.5% paste in olive oil (w/w), and was not a sensitizer in a GPMT. Dimyristyl phosphate, applied under an occlusive patch for 4 h, was not irritating to rabbit skin, nor was it an irritant or sensitizer in guinea pigs at a concentration of 75% in distilled water.

C20-22 alkyl phosphate, 5% in an emulsion, was not an irritant or a sensitizer in an HRIPT completed in 49 subjects. In an HRIPT completed in 108 subjects, a hair cream containing 1.0% dicetyl phosphate was not a sensitizer.

Some of the alkyl phosphates are reported to be ocular irritants. A 10% solution of potassium lauryl phosphate, tested as a 50% dilution in the HET-CAM, demonstrated moderate ocular irritation potential, and oleyl phosphate demonstrated the potential to be corrosive and a severe ocular irritant in an *in vitro* eye corrosives and severe irritants study. In rabbit eyes, potassium lauryl phosphate was an irritant, C20-22 alkyl phosphate was a moderate irritant, and dicetyl phosphate was slightly irritating. However, a 3% potassium cetyl phosphate solution, tested as a 50% dilution in a HET-CAM, demonstrated practically no ocular irritation potential, and *phosphoric acid, C16-18 alkyl esters, potassium salts* and dimyristyl phosphate[35] were classified as non-irritating to rabbit eyes.

DISCUSSION

The Panel reviewed the safety of 28 ingredients in the alkyl phosphate family; these ingredients share a common phosphate core structure, varying by the identity of the alkyl chains attached. The Panel acknowledged that much of the data were obtained from ECHA summaries, and in several instances, structural analogs were used as supporting substances to provide read-across. The Panel found this read-across appropriate to support the safety of the alkyl phosphates named in this report because the analogs contained chain lengths distributions that had a great deal of overlap with the alkyl phosphates.

The Panel noted there were little to no safety test data on the triester phosphates included in this safety assessment. However, based on the molecular weights of the triesters (≥603), and the calculated log P values (≥17.02), the Panel

does not expect these ingredients to penetrate the skin. Therefore, the Panel determined that it was appropriate to include the triesters among the ingredients in this safety assessment, and to conclude on their safety.

The Panel also noted that there were no impurities data. Based on the method of manufacture and the absence of adverse effects in repeat oral toxicity studies, the Panel was not concerned about the absence of these data.

Finally, the Panel was concerned that the potential exists for ocular and/or dermal irritation with the use of products formulated using alkyl phosphates, and the Panel specified that products containing alkyl phosphates must be formulated to be non-irritating. Specifically, the Panel recognized the potential for ocular irritation when potassium cetyl phosphate is used at up to 8.3% in mascara products. Additionally, some of the alkyl phosphates were irritating to the skin of animals; however, these studies were conducted with concentrations that were much greater than the concentrations reported to be used in cosmetics.

CONCLUSION

The CIR Expert Panel concluded the following 28 alkyl phosphates are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating:

Potassium Cetyl Phosphate
Potassium C9-15 Alkyl Phosphate
Potassium C11-15 Alkyl Phosphate*
Potassium C12-13 Alkyl Phosphate
Potassium C12-14 Alkyl Phosphate*
Potassium Lauryl Phosphate
C8-10 Alkyl Ethyl Phosphate*
C9-15 Alkyl Phosphate
C20-22 Alkyl Phosphate
Castor Oil Phosphate
Cetearyl Phosphate*
Cetyl Phosphate
Disodium Lauryl Phosphate*
Disodium Oleyl Phosphate*
Lauryl Phosphate
Myristyl Phosphate*
Octyldecyl Phosphate*
Oleyl Ethyl Phosphate*
Oleyl Phosphate*
Sodium Lauryl Phosphate*
Stearyl Phosphate
Dicetyl Phosphate
Dimyristyl Phosphate*
Dioleyl Phosphate
Tricetyl Phosphate*
Trilauryl Phosphate*
Trioleyl Phosphate
Tristearyl Phosphate*

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

TABLES

Table 1. Definitions and functions of the ingredients in this safety assessment

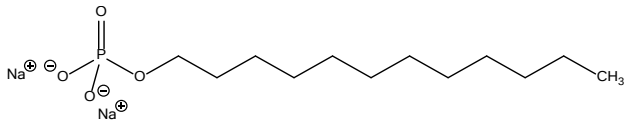
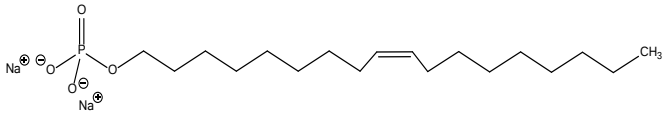
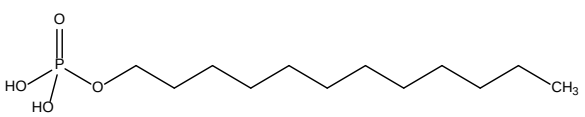
Ingredient (CAS No.)	Definition[1]	Function(s)[1]
Potassium Cetyl Phosphate 90506-45-9 (generic); 17026-85-6; 19035-79-1; 84861-79-0	the potassium salt of a complex mixture of esters of phosphoric acid and cetyl alcohol; R, R', and R" of Figure 1 may be cetyl, hydrogen, or electron pairs with potassium cations	surfactant – emulsifying agent
Potassium C9-15 Alkyl Phosphate 190454-07-0	the potassium salt of a complex mixture of esters of synthetic C9-15 alcohols with phosphoric acid; R, R', and R" of Figure 1 may be nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hydrogen, or electron pairs with potassium cations	surfactant – cleansing agent
Potassium C11-15 Alkyl Phosphate	the potassium salt of the phosphoric ester of C11-15 alcohol; R, R', and R" of Figure 1 may be undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hydrogen, or electron pairs with potassium cations	surfactant – cleansing agent; surfactant – emulsifying agent
Potassium C12-13 Alkyl Phosphate	the potassium salt of a complex mixture of esters of phosphoric acid and C12-13 alcohols; R, R', and R" of Figure 1 may be dodecyl, tridecyl, hydrogen, or electron pairs with potassium cations	surfactant – cleansing agent
Potassium C12-14 Alkyl Phosphate	the potassium salt of a complex mixture of esters of phosphoric acid and a synthetic fatty alcohol containing 12 to 14 carbons in the alkyl chain; R, R', and R" of Figure 1 may be dodecyl, tridecyl, tetradecyl, hydrogen, or electron pairs with potassium cations.	surfactant – cleansing agent
Potassium Lauryl Phosphate 39322-78-6	the potassium salt of lauryl phosphate; R, R', and R" of Figure 1 may be lauryl, hydrogen, or electron pairs with potassium cations	surfactant – cleansing agent
C8-10 Alkyl Ethyl Phosphate 68412-60-2	a mixture of phosphate esters of C8-10 alcohols and ethyl alcohol; R, R', and R" of Figure 1 may be ethyl, octyl, nonyl, decyl, hydrogen, or electron pairs with potassium cations	viscosity increasing agent – non-aqueous
C9-15 Alkyl Phosphate 190454-07-0	a complex mixture of esters of synthetic C9-15 alcohols with phosphoric acid; R, R', and R" of Figure 1 may be nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, or hydrogen	surfactant – cleansing agent; surfactant – emulsifying agent
C20-22 Alkyl Phosphate 84962-18-5	a complex mixture of esters of phosphoric acid and C20-22 alcohols; R, R', and R" of Figure 1 may be eicosyl, heneicosyl, docosyl, or hydrogen	surfactant – emulsifying agent
Castor Oil Phosphate	a complex mixture of esters of ricinus communis (castor) seed oil and phosphoric acid; R, R', and R" of Figure 1 may be the fatty alcohol residues of castor oil, or hydrogen	anticaking agent; emulsion stabilizer
Cetearyl Phosphate 90506-73-3	a complex mixture of esters of cetearyl alcohol and phosphoric acid; R, R', and R" of Figure 1 may be cetyl, stearyl, or hydrogen	skin conditioning agent – miscellaneous
Cetyl Phosphate 3539-43-3	a complex mixture of esters of phosphoric acid and cetyl alcohol; R, R', and R" of Figure 1 may be cetyl or hydrogen	surfactant – emulsifying agent
Disodium Lauryl Phosphate 7423-32-7	the disodium salt of lauryl phosphate 	surfactant – emulsifying agent
Disodium Oleyl Phosphate	is the organic salt that conforms generally to the formula: 	surfactant – cleansing agent; surfactant – emulsifying agent
Lauryl Phosphate 12751-23-4; 2627-35-2	the monolauryl ester of phosphoric acid 	surfactant – emulsifying agent

Table 1. Definitions and functions of the ingredients in this safety assessment

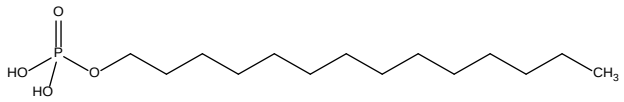
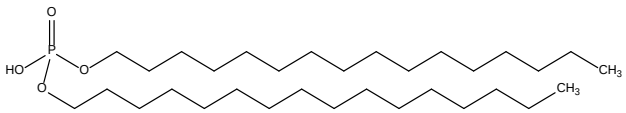
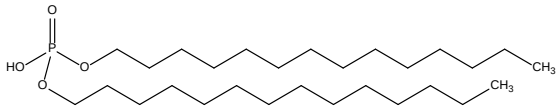
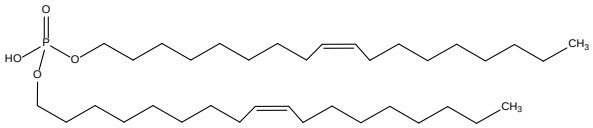
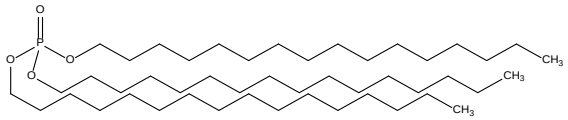
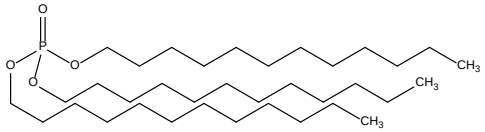
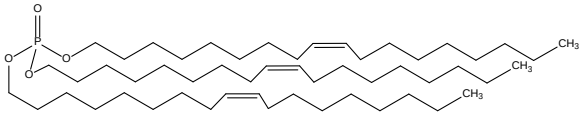
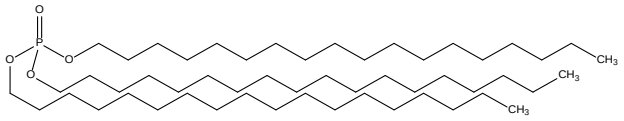
Ingredient (CAS No.)	Definition[1]	Function(s)[1]
Myristyl Phosphate 10054-29-2	the organic compound that conforms to the formula: 	oral care agent; surfactant – cleansing agent; surfactant – foam booster
Octyldecyl Phosphate 97553-81-6	a complex mixture of esters of phosphoric acid and octyldecanol; R, R', and R" of Figure 1 may be the 2-octyldecyl or hydrogen	surfactant – emulsifying agent
Oleyl Ethyl Phosphate 10483-96-2	a complex mixture of phosphate esters of oleyl and ethyl alcohols; R, R', and R" of Figure 1 may be ethyl, oleyl, or hydrogen	surfactant – emulsifying agent
Oleyl Phosphate 37310-83-1	a mixture of mono- and diesters of oleyl alcohol and phosphoric acid; R, R', and R" of Figure 1 may be oleyl or hydrogen	surfactant – emulsifying agent
Sodium Lauryl Phosphate 50957-96-5[36]	the sodium salt of a complex mixture of esters of lauryl alcohol and phosphoric acid; R, R', and R" of Figure 1 may be lauryl, hydrogen, or electron pairs with sodium cations	surfactant – cleansing agent; surfactant – emulsifying agent
Stearyl Phosphate 2958-09-0	a mixture of mono- and diesters of stearyl alcohol and phosphoric acid; R, R', and R" of Figure 1 may be stearyl or hydrogen	surfactant – emulsifying agent
Dicetyl Phosphate 2197-63-9	a complex mixture of diesters of cetyl alcohol and phosphoric acid 	surfactant – emulsifying agent
Dimyristyl Phosphate 6640-03-5	a complex mixture of diesters of myristyl alcohol and phosphoric acid 	surfactant – cleansing agent; surfactant – emulsifying agent
Dioleyl Phosphate 14450-07-8	a complex mixture of esters of oleyl alcohol and phosphoric acid 	emulsion stabilizer; hair conditioning agent; surfactant – emulsifying agent; surfactant – stabilizing agent; pH adjuster
Tricetyl Phosphate 56827-95-3 68814-13-1	the triester of phosphoric acid and cetyl alcohol. It conforms to the formula: 	plasticizer
Trilauryl Phosphate 682-49-5	the triester of phosphoric acid and lauryl alcohol 	plasticizer; skin conditioning agent – occlusive
Trioleyl Phosphate 3305-68-8	the triester of phosphoric acid and oleyl alcohol that conforms generally to the formula: 	plasticizer; skin conditioning agent – occlusive
Tristearyl Phosphate 4889-45-6	the triester of phosphoric acid and stearyl alcohol 	plasticizer

Table 2. Chemical and Physical Properties

Property	Description	Reference
	Potassium Cetyl Phosphate	
physical characteristics	white to off-white powder, with no or a weakly fatty odor	3
molecular weight	359.5	37
solubility	readily soluble in tepid water; soluble in the heated oil phase	3
acid value	270-295	3
pH	6.5-8 (1% in water)	3
	Potassium Lauryl Phosphate	
physical characteristics	solid white paste	19
molecular weight	304.4	38
solubility	slightly soluble in water	19
density	1.07 g/cm^3 (22^{o}C)	19
log P_{ow}	2.74	19
	C20-22 Alkyl Phosphate	
molecular weight	≥378.53	6
melting point	70-75^{o}C	6
solubility	≤1 x 10^{-3} g/l (20^{o}C)	6
specific gravity	0.6	6
density	870 kg/m³ (25^{o}C)	20
particle size distribution	ca. 2.8 mm ≤1.44 mm – 12.2% 1.4 mm - ≤2 mm – 33.8% 2 mm - ≤2.8 mm – 32.1% 2.8 mm - ≤4 mm – 21.8%	20
	Cetyl Phosphate	
molecular weight	322	38
boiling point	439.8^{o}C	38
log P (predicted)	6.38 ± 0.21	38
	Lauryl Phosphate	
physical characteristics	solid	39
melting point	47^{o}C	39
solubility	not soluble in water in paraffin, soy oil, or isopropyl palmitate: not soluble at room temperature; clear solution at 80^{o}C	39
	Octyldecyl Phosphate	
physical characteristics	liquid	39
melting point	<0^{o}C	39
solubility	not soluble in water; clear solution in paraffin, soy oil, or isopropyl palmitate at room temperature and at 80^{o}C	39
	Oleyl Phosphate	
physical characteristics	dark brown, high viscous liquid with a slightly castor oil-like odor waxy solid	21 39
molecular weight	348.5	38
melting range	-77 to 53^{o}C 45^{o}C	21 39
boiling point	477.9^o	38
solubility	poorly water soluble in paraffin, soy oil, or isopropyl palmitate: not soluble at room temperature; clear solution at 80^{o}C	21 39
log K_{ow}	>1	21
density	1.01 g/cm^3 (at 20^{o}C)	21
	Stearyl Phosphate	
physical characteristics	solid	39
molecular weight	350	38
melting point	62^{o}C	39
boiling point	465.6^{o}C	38
solubility	not soluble in water in paraffin, soy oil, or isopropyl palmitate: not soluble at room temperature; clear solution at 80^{o}C	39
log P (calculated)	7.44 ± 0.21	38
	Dicetyl Phosphate	
physical characteristics	solid white flakes	22
molecular weight	546.8	38
boiling point	600.4^{o}C	38

Table 2. Chemical and Physical Properties

Property	Description	Reference
log P (calculated)	14.95± 0.58	[38]
	Dimyristyl Phosphate	
molecular weight	490.7	[38]
boiling point	555.5°C	[38]
log P (calculated)	12.83± 0.58	[38]
	Dioleyl Phosphate	
molecular weight	626.9	[38]
boiling point	680.1°C	[38]
log P (calculated)	14.212	[38]
	Tricetyl Phosphate	
molecular weight	771.3	[38]
boiling point	616.5°C	[38]
log P (calculated)	22.172	[38]
	Trilauryl Phosphate	
molecular weight	603	[38]
boiling point	522.2°C	[38]
log P (calculated)	17.02	[38]
	Trioleyl Phosphate	
molecular weight	849.4	[38]
boiling point	805.2°C	[38]
log P (calculated)	25.027	[38]
	Tristearyl Phosphate	
molecular weight	855.4	[38]
boiling point	660°C	[38]
log P (calculated)	225.229	[38]

Table 3. Frequency and concentration of use according to duration and type of exposure

	# of Uses[7]	*Max. Conc. of Use (%)*[8,9]	*# of Uses*[7]	*Max. Conc. of Use (%)*[8,9]	*# of Uses*[7]	*Max. Conc. of Use (%)*[8,9]
	Potassium Cetyl Phosphate		**Potassium C9-15 Alkyl Phosphate**		**Potassium C12-13 Alkyl Phosphate**	
Totals*	**375**	**0.05-8.3**	**NR**	**0.001**	**2**	**6.5**
Duration of Use						
Leave-On	*341*	*0.05-8.3*	*NR*	*NR*	*2*	*NR*
Rinse Off	*30*	*0.5-1*	*NR*	*0.001*	*NR*	*6.5*
Diluted for (Bath) Use	*4*	*NR*	*NR*	*NR*	*NR*	*6.5*
Exposure Type						
Eye Area	66	0.6-8.3	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1; 129[a]; 96[b]	0.3[a]	NR	NR	NR	NR
Incidental Inhalation-Powder	1; 96[b]; 5[c]	0.14-3[c]	NR	NR	NR	NR
Dermal Contact	329	0.05-3	NR	NR	2	6.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.001	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR
Mucous Membrane	7	0.55	NR	NR	NR	6.5
Baby Products	5	NR	NR	NR	NR	NR

Table 3. Frequency and concentration of use according to duration and type of exposure

	# of Uses[7]	Max. Conc. of Use (%)[8,9]	# of Uses[7]	Max. Conc. of Use (%)[8,9]	# of Uses[7]	Max. Conc. of Use (%)[8,9]
	Potassium Lauryl Phosphate		**C9-15 Alkyl Phosphate**		**C20-22 Alkyl Phosphate**	
Totals*	**4**	**NR**	**13**	**0.0011-0.12**	**14**	**0.55-1.7**
Duration of Use						
Leave-On	*3*	*NR*	*8*	*0.0011-0.12*	*13*	*0.55-1.7*
Rinse Off	*1*	*NR*	*5*	*0.0044-0.12*	*1*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	2	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	3[b]	NR	4[a]; 1[b]	NR	7[a]; 3[b]	NR
Incidental Inhalation-Powder	3[b]	NR	1[b]	0.12[c]	3[b]	0.55-1.7[c]
Dermal Contact	4	NR	13	0.0011-0.12	14	0.55-1.7
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	1	0.0044	NR	NR
Baby Products	NR	NR	NR	NR	NR	1.1
	Castor Oil Phosphate		**Cetyl Phosphate**		**Lauryl Phosphate**	
Totals*	**2**	**NR**	**94**	**0.14-2**	**2**	**0.25-8.7**
Duration of Use						
Leave-On	*2*	*NR*	*85*	*0.14-2*	*NR*	*3.8*
Rinse Off	*NR*	*NR*	*9*	*0.5-1*	*2*	*0.25-8.7*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	1	NR	7	0.14-2	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	2[a]	NR	1; 26[a]; 47[b]	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	47[b]	0.25-2[b]	NR	3.8[c]
Dermal Contact	2	NR	93	0.25-2	2	0.25-8.7
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Stearyl Phosphate		**Dicetyl Phosphate**		**Dioleyl Phosphate**	
Totals*	**1**	**NR**	**109**	**0.038-4**	**1**	**0.4-1.5**
Duration of Use						
Leave-On	*1*	*NR*	*60*	*0.2-4*	*NR*	*NR*
Rinse Off	*NR*	*NR*	*49*	*0.038-1*	*1*	*0.4-1.5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NS*	*NR*	*NR*
Exposure Type						
Eye Area	1	NR	8	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	1; 13[a]; 14[c]	0.2-0.8[a]	NR	NR
Incidental Inhalation-Powder	NR	NR	14[c]	NR	NR	NR
Dermal Contact	1	NR	31	0.26-4	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	29	0.038-1	NR	0.4
Hair-Coloring	NR	NR	41	0.13-0.9	1	1.5
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Trioleyl Phosphate					
Totals*	**3**	**0.02-4.2**				
Duration of Use						
Leave-On	*3*	*0.02-4.2*				
Rinse Off	*NR*	*NR*				
Diluted for (Bath) Use	*NR*	*NR*				
Exposure Type						
Eye Area	NR	NR				
Incidental Ingestion	3	0.02-1				
Incidental Inhalation-Spray	NR	NR				
Incidental Inhalation-Powder	NR	NR				
Dermal Contact	NR	4.2				
Deodorant (underarm)	NR	NR				
Hair - Non-Coloring	NR	NR				
Hair-Coloring	NR	NR				
Nail	NR	NR				
Mucous Membrane	3	0.02-1				
Baby Products	NR	NR				

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

[a] Includes products that can be sprays, but it is not known whether the reported uses are sprays

[b] Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation

[c] Includes products that can be powders, but it is not known whether the reported uses are powders

NR – none reported

NS – survey results not yet received

Table 4. Ingredients Not Reported to be Used

Potassium C11-15 Alkyl Phosphate
Potassium C12-14 Alkyl Phosphate
C8-10 Alkyl Ethyl Phosphate
Cetearyl Phosphate
Disodium Lauryl Phosphate
Disodium Oleyl Phosphate
Myristyl Phosphate
Octyldecyl Phosphate
Oleyl Ethyl Phosphate
Oleyl Phosphate
Sodium Lauryl Phosphate
Dimyristyl Phosphate
Tricetyl Phosphate
Trilauryl Phosphate
Tristearyl Phosphate

Table 5. Single-Dose toxicity studies

Test Article	Animals/Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/LC_{50} Results	Reference
			DERMAL		
C20-22 alkyl phosphate	5 Sprague-Dawley rats/sex	paraffin oil	2 g/kg bw (10 ml/kg bw) applied using a 24-h semi-occlusive patch - negative controls were exposed to distilled water	>2 g/kg bw - no cutaneous reactions or signs of toxicity were observed	20
oleyl phosphate	5 Wistar rats/sex	applied neat	2 g/kg applied using a 24-h semi-occlusive patch	>2 g/kg bw - slight to severe erythema, slight edema, and other signs of irritation (e.g., wounds, crusting, and desquamation) were observed until study termination at day 14 in males and up to day 11 in females	21
dicetyl phosphate, 80% paste	10 Sprague-Dawley rats/sex	distilled water	2 g/kg using 24-h occlusive patch; 4.4 ml/kg were applied - the test area was 5 cm^2	>2 g/kg bw - no signs of toxicity were observed	22
dicetyl phosphate, 45.45% paste	5 Sprague-Dawley rats/sex	olive oil	2 g/kg applied for 24 h under an adhesive bandage	> 2 g/kg - no erythema or edema were observed - no clinical signs of toxicity	23
			ORAL		
1-octadecanol, phosphate, potassium salt	4 Wistar rats	water	2 g/kg by gavage	> 2 g/kg	22
potassium C9-15 alkyl phosphate	5 Sprague-Dawley rats/sex	none	2 g/kg (0.723 g/kg bw a.i.) by gavage	> 2 g/kg (0.723 g/kg bw a.i.) - no animals died during the study - piloerection, hunched posture, and other signs of toxicity were observed during the first three days	22
potassium lauryl phosphate, 25%	10 female rats	water	6.3-15.0 g/kg bw by gavage	10.49 g/kg	19
C20-22 alkyl phosphate	5 Sprague-Dawley rats/sex	paraffin oil	2 g/kg by gavage	> 2 g/kg	20
cetyl phosphate, 10%	10 Sprague-Dawley rats/sex	distilled water	4.7 g/kg by gavage	>4.7 g/kg bw - two females of the 4700 mg/kg bw group died during the study	22
oleyl phosphate	3 female Wistar rats	sunflower oil	2 g/kg bw, by gavage	> 2 g/kg	21
dicetyl phosphate, 25% suspension	5 OF1 mice/sex	olive oil	5 g/kg, by gavage	> 5 g/kg no signs of toxicity; no mortality	25
dicetyl phosphate, 25% suspension	5 Sprague-Dawley rats/sex	olive oil	5 g/kg, by gavage	> 5 g/kg no signs of toxicity; no mortality	26
dimyristyl phosphate	5 Sprague-Dawley rats/sex	distilled water	2 g/kg, by gavage	> 2 g/kg no signs of toxicity; no mortality	24
			INHALATION		
1% aq. *phosphoric acid, C16-18 alkyl esters, potassium salts*	10 Wistar rats/sex	in emulsion	200 µl/L nose-only exposure for 4 h; the nebulizing nozzle produced an aerosol with particle sizes of 2-5 µm	>200 µl/L - one animal died within 24 h of dosing	22

Abbreviations: a.i. – active ingredient

Table 6. Repeated Dose Toxicity Studies

Test Article	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
			ORAL			
potassium lauryl phosphate	3 Wistar rats/sex	14 days	water	0, 60, 600, or 1000 mg/kg bw/day; by gavage	NOAEL = 600 mg/kg bw/day (males and females) - all animals survived until study termination - piloerection was observed in a few females of the high-dose group - slight decrease in absolute prostate weights and a slight increase in absolute and relative (to brain and to body) epididymis weights was observed in high dose males - slight-to-moderate increase in neutrophils, with a concurrent slight decrease in lymphocytes,, and a slight, dose-dependent, increase in serum alkaline phosphatase levels, was reported in male and female high-dose animals	19
C20-22 alkyl phosphate	3 Sprague-Dawley rats/sex	14 days	olive oil	0, 100, 300, or 1000 mg/kg bw/day, by gavage	- all animals survived until study termination - no macroscopic observations -slight decrease in feed consumption during wk 2 in the mid- and high-dose females compared to controls	20
sodium lauryl phosphate	rats (no./group not provided)	14 days	not specified	125, 250, 500, or 1000 mg/kg bw/day (no other details provided)	- no adverse effects were reported at any dose (no other details were provided)	19
myristyl phosphate	5 Sprague-Dawley rats/sex	28 days	in feed	0, 227, 505, or 1564 mg/kg bw/day, in feed	NOEL = 1564 mg/kg bw/day (males); 227 mg/kg bw/day (females) NOAEL = 1564 mg/kg bw/day (females) - all animals survived until study termination; no clinical signs of toxicity - an increased incidence in focal corticomedullary mineralization was observed in mid- and high-dose female rats, but not in controls, and could be treatment-related - no other dose-related or toxicologically-significant changes were observed	22
oleyl phosphate	5 Wistar rats/sex	28 days	sunflower oil	0, 100, 300, or 1000 mg/kg bw/day	NOAEL = 1000 mg/kg bw/day (males and females) - no signs of toxicity were observed, and no animals died during the observation period - no effects on clinical chemistry or hematology parameters; no test-article-related gross or microscopic lesions were observed, and organ weights were similar in test and control animals	21
potassium C9-15 alkyl phosphate (34.35% a.i.)	10 Sprague-Dawley rats/sex 5/sex in the control and high-dose recovery groups	91 days dosing; 14-day recovery period	purified water	0, 8, 40, 200, and 1000 mg/kg bw/day; by gavage	BMDL10 = 240.3 mg/kg bw/day (males and females) BMD = 374.61 mg/kg bw/day - no animals died prior to study termination; some clinical signs, including salivation and respiratory sounds were noted in some animals during the testing period, but not in recovery animals -mild-to-marked hyperplasia of squamous epithelium in the forestomach of high-dose test, but not recovery, animals - mild hypertrophy in some 200 mg/kg bw animals, and mild-to-moderate hypertrophy of the cortical glomerular zone of the adrenal gland in most of the high-dose test animals; mild changes observed in recovery animals	22

Abbreviations: a.i. – active ingredient; BMD – benchmark dose; BMDL - benchmark dose lower confidence limit; NOAEL – no-observable adverse effect level; NOEL - no-observed effect level

Table 7. Reproductive and developmental toxicity studies

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
			ORAL			
potassium C9-15 alkyl phosphate (36.1% potassium salt)	25 gravid female Sprague-Dawley rats	deionized water	0, 36.1, 180.5, or 361 mg/kg bw/day (a.i.)	animals were dosed by gavage on days 6-15 of gestation - the dams were killed on day 20 of gestation	not embryotoxic, fetotoxic, or teratogenic - NOELs for developmental toxicity, embryotoxicity, fetotoxicity, and teratogenicity were 361 mg/kg bw/day (a.i.) - NOEL and NOAEL for maternal toxicity were 36.1 and 361 mg/ kg bw/day (a.i.), respectively - all animals survived until study termination - most common clinical sign reported was rales	[22]
C20-22 alkyl phosphate	10 Sprague-Dawley rats/sex	olive oil	0, 100, 300, or 1000 mg/kg bw/day	dosed by gavage - males were dosed from 2 wks prior to mating until the end of mating; females from 2 wks prior to mating until day 5 post-partum - observations and examinations included gross observations, body weights and feed consumption, clinical chemistry, hematology, neurobehavior, gross pathology, estrous cyclicity, parental and neonatal gross necropsy, and parental histopathology and organ weights	not a reproductive toxicant - NOELs for reproduction (mating and fertility) and neonatal toxicity were 1000 mg/kg bw/day - NOAEL for parental toxicity was 1000 mg/kg bw/day - no notable effects were reported in any of the parameters examined - no treatment-related mortality was observed	[20]
oleyl phosphate	12 Wistar rats/sex	sunflower oil	0, 100, 300, or 1000 mg/kg bw/day	dosed once daily by gavage - males were dosed for 14 days prior to mating until necropsy (41 days total dosing period) - females were dosed 14 days prior to mating, through the gestation period, and up to lactation day 3, 4 or 5 (41 – 46 days total)	not a reproductive toxicant - NOAELs for maternal toxicity and reproductive performance in males and females, and for development in F_1 offspring, were 1000 mg/kg bw/day - no toxic effects - no negative effect on reproductive parameters - no effects in neonate development were noted	[21]
sodium lauryl phosphate	main group: 12 Sprague-Dawley rats/sex recovery group: 5 rats/sex	olive oil	main group: 0, 250, 500, or 1000 mg/kg bw/day 14-day recovery group: 0 or 1000 mg/kg bw/day	dosed by gavage - the males of the main group and the males and females of the recovery groups were dosed 14 days prior to, 14 days during, and 14 days after mating - the females of the main group were dosed from 14 days prior to mating through day 4 of lactation	no reproductive or developmental effects were observed - NOEL for the F_1 generation was 1000 mg/kg bw/day - NOAEL for parental male and female animals was 1000 mg/kg bw/day - the test substance had an irritant effect on the stomachs of animals of all dose groups, causing local effects on the forestomach mucosa; no other dose-related toxic effects were observed	[19]

Abbreviations: a.i. – active ingredient; NOAEL – no-observable adverse effect level; NOEL – no-observed effect level

Table 8. Genotoxicity studies

Test Article	Concentration/Dose/Vehicle	Procedure	Test System	Results	Reference
		IN VITRO			
1-octadecanol, phosphate, potassium salt	0.051 – 5.009 mg/plate vehicle: sterile water	Ames test, with and without metabolic activation; negative and positive controls were used	*Salmonella typhimurium* TA97a; TA98; TA100; TA102; TA1535	negative; controls gave valid results	[22]
potassium lauryl phosphate	*S. typhimurium*: ≤2500 µg/plate without and ≤5000 µg/plate with metabolic activation *Escherichia coli*: ≤5000 µg/plate with and without metabolic activation vehicle: deionized water	Ames test, with and without metabolic activation; negative and positive controls were used	*S. typhimurium* TA1535, TA1537, TA98, and TA100 *E. coli* WP2 uvrA	negative	[19]
potassium lauryl phosphate	≤2000 µg/ml without and ≤1500 µg/ml with metabolic activation vehicle: cell culture medium	mammalian cell gene mutation assay, with and without metabolic activation; negative and positive controls were used (2 runs)	Chinese hamster lung fibroblast V79 cells	negative	[19]
potassium lauryl phosphate	≤1000 µg/ml without and ≤1800 µg/ml with metabolic activation vehicle: cell culture medium	chromosomal aberration assay, with and without metabolic activation; negative and positive controls were used (2 runs)	Chinese hamster lung fibroblast V79 cells	negative	[19]
C20-22 alkyl phosphate	50-5000 µg/plate vehicle: acetone	Ames test, with and without metabolic activation; negative and positive controls were used	*S. typhimurium* TA1535, TA1537, TA98, and TA100 *E. coli* WP2 uvrA	negative; controls gave valid results	[20]
C20-22 alkyl phosphate	0.0313-0.5 µg/ml vehicle: ethanol	mammalian cell gene mutation assay, with and without metabolic activation; negative and positive controls were used	mouse lymphoma L5178Y TK +/- cells	negative; controls gave valid results	[20]
C20-22 alkyl phosphate	0.0625-1 µg/ml vehicle: ethanol	chromosomal aberration assay, with and without metabolic activation; negative and positive controls were used	human male peripheral blood lymphocytes	negative; controls gave valid results	[20]
cetyl phosphate	0.0316-1750 µg/ml, without activation 0.010-2500 µg/ml, with activation (cell culture medium)	mammalian cell gene mutation assay; with and without metabolic activation	Chinese hamster lung fibroblasts (V79)	negative	[22]
oleyl phosphate	*S. typhimurium*: ≤50 µg/plate without and ≤5000 µg/plate with metabolic activation *Escherichia coli*: ≤5000 µg/plate with and without metabolic activation vehicle: not identified	Ames test, with and without metabolic activation; negative and positive controls were used	*S. typhimurium* TA1535, TA1537, TA98, and TA100 *E. coli* WP2 uvrA	negative	[21]
oleyl phosphate	≤75 µg/ml without and ≤130 µg/ml with metabolic activation vehicle: DMSO	mammalian cell gene mutation assay, with and without metabolic activation; negative and positive controls were used	Chinese hamster ovary cells	negative	[21]
oleyl phosphate	≤45 µg/ml without and ≤110 µg/ml with metabolic activation vehicle: DMSO	chromosomal aberration assay, with and without metabolic activation; negative and positive controls were used	Chinese hamster lung fibroblast V79 cells	negative	[21]

Abbreviations: DMSO – dimethyl sulfoxide

Table 9. Irritation and sensitization studies

Test Article	Concentration/Dose	Test Pop.	Procedure	Results	Reference
			ALTERNATIVE STUDIES		
oleyl phosphate	not specified	EpiSkin model	performed according to OECD Guideline 439 and EU method B.46 applied to reconstituted human epidermis for 15 minutes, and the effect on cell viability was compared to that of the negative control (water)	did not demonstrate skin irritation potential -cell viability results were above 50% when compared to the viability values obtained from the negative control	21
oleyl phosphate	not specified	*in vitro* membrane barrier	Corrositex® model; the test was performed according to OECD Guideline 435 and INVITTOX protocol no. 116 - citric acid, 10% aq., was used as a negative control and sodium hydroxide as a positive control	no potential for skin corrosion	21
			NON-HUMAN		
phosphoric acid, C16-18 alkyl esters, potassium salts	neat; 0.5 ml	6 NZW rabbits	24-h occlusive patch applied to a 2.5 cm^2 area of both clipped intact and abraded skin; the test sites were scored at 24 and 72 h using the Draize scale	24 h: 4/6 animals had an erythema score of 1/4 at the abraded site; no edema 72 h; no erythema or edema	22
potassium lauryl phosphate	77% paste in water; 0.5 ml; 500 mg	3 NZW rabbits	4-h semi-occlusive patch applied to a 2.5 cm^2 area of shaved skin	irritating 72 h after patch removal: mean irritation score of 2.89/4 for erythema and 1.33/4 for edema -effects were fully reversible by day 21	19
potassium lauryl phosphate	paste in 0.9% sodium chloride solution (concentration not specified); 500 mg	6 albino Russian rabbits	24-h occlusive patches applied to a 2.5 cm^2 area of clipped skin;	highly irritating primary dermal irritation index was 6.67 at 72 h	19
potassium lauryl phosphate	intradermal induction: 1% epidermal induction: 75% challenge: 10%	female Dunkin-Hartley guinea pigs; 10 test and 5 control	GPMT - intradermal induction on day 1; epidermal induction (occlusive patch) on day 8; epidermal challenge (occlusive patch) on day 22 - vehicles used during epicutaneous induction were FCA with physiological saline and purified water; purified water served as the vehicle with the dermal patches	not a sensitizer	19
C20-22 alkyl phosphate	applied neat, 0.5 g/animal	3 female albino rabbits	dermal irritation/corrosion study (OECD Guideline 404) - 4-h occlusive patch applied to shaved skin	not an irritant - no erythema or edema at any time; primary skin irritation score of 0 at each observation	20
C20-22 alkyl phosphate	intradermal induction: 3.125% in olive oil topical induction: 100% challenge: 50% in liquid paraffin and undiluted	11 female Dunkin-Hartley guinea pigs	GPMT - intradermal induction: 3 series of 2 x 0.1 ml of 50% FCA, test article, or 50/50 solution of test article + FCA - topical induction, day 8: 48 h occlusive patch, 0.5 ml - challenge, day 21: 24 h occlusive patch, 0.5 ml - included a vehicle control group	not a sensitizer - one animal had slight erythema 24 and 48 h after challenge with undiluted test article	20

Table 9. Irritation and sensitization studies

Test Article	Concentration/Dose	Test Pop.	Procedure	Results	Reference
cetyl phosphate	intradermal induction: 0.5% in water epidermal induction: 40% challenge 1: 20% and 40% challenge 2: 1% and 10% vehicle: distilled water	female Dunkin-Hartley guinea pigs; 20 test and 10 control	GPMT - intradermal induction on day 1; epidermal induction (48-h occlusive patch) 24 h after intradermal induction; epidermal challenge 1 (48-h occlusive patch) 2 wks after induction; challenge 2 (24-h occlusive patch) 1 wk after challenge 1	not a sensitizer - 20% challenge: slight erythema in 8/20 test and 4/10 negative control animals after 24 h 40% challenge: slight erythema in 13/20 test and 7/10 negative control animals after 24 h - with the exception of the 20% negative controls, reactions persisted in all of these groups at 72	22
lauryl phosphate	intradermal induction: 0.25% epidermal induction: 12.5% challenge: 0.25% and 0.5%	female Dunkin-Hartley guinea pigs; 20 test and 10 control	GPMT - intradermal induction on day 1; epidermal induction (48-h occlusive patch) 24 h after intradermal induction; epidermal challenge (24-h occlusive patches) 2 wks after induction	not a sensitizer -12.5% induction dose was irritating, but no reactions were observed at challenge	22
oleyl phosphate	undiluted; 2000 mg/kg	5 Wistar rats/sex	24-h semi-occlusive patch (previously cited in the single-dose toxicity table)	irritating slight to severe erythema, slight edema, and other signs of irritation (e.g., wounds, crusting, and desquamation) were observed until study termination at day 14 in males and up to day 11 in females (as reported in the single-dose toxicity table)	21
oleyl phosphate	10%, 25%, 50%, and 75% in DMF	female CBA/Ca mice, 1or 2/grp	preliminary irritation study for LLNA (details not provided)	significant irritation	21
oleyl phosphate	0, 0.5%, 1%, 2.5%, and 5.0% (w/v) in DMF	5 female CBA/Ca mice	LLNA; performed according to OECD Guideline 429, EU method B.42, and EPA OPPTS 870.2600 positive controls were used	no potential for sensitization; ≤5% oleyl phosphate did not increase lymphoproliferation compared to the negative controls - not irritating	21
dicetyl phosphate	0.5 g test article, prepared as a paste in 0.575 g olive oil (calculated as 46.5% w/w)	6 male NZW rabbits	4-h semi-occlusive patch to intact skin; 1.2 ml of preparation test sites were scored 1, 24, 48, and 72 h after patch removal	non-irritating; slight desquamation of the epidermis at the application site - mean erythema score – 0.56 - mean edema score – 0.0	27
dicetyl phosphate	80% paste in distilled water; 2000 mg/kg	10 Sprague-Dawley rats/sex	24-h occlusive patch (previously cited in the single-dose toxicity table)	not irritating (as reported in the single-dose toxicity table)	22
dicetyl phosphate	intradermal induction: 5% in liquid paraffin epidermal induction: 50% paste with liquid paraffin epidermal challenge: 50% paste with liquid paraffin	10 Dunkin-Hartley guinea pigs/sex/group	GPMT - intradermal induction: 3 series of 2 x 0.1 ml of FCA, test article, or 50/50 solution of test article + FCA - 0.5 ml 10% SLS was painted on skin on day 8 - epidermal induction, day 9: 48 h occlusive patch, 0.5 ml - challenge, 11 days after induction: 24 h occlusive patch, 0.5 ml - included a test-article control group (i.e., vehicle at induction and test article at challenge) and a positive control group (i.e., 0.05% DNCB)	not a sensitizer; no cutaneous intolerance - 2 test-article related mortality - weak to moderate irritation was reported in a preliminary study with injection of 1, 2.5, and 5% test article (4 animals)	28

Table 9. Irritation and sensitization studies

Test Article	Concentration/Dose	Test Pop.	Procedure	Results	Reference
dimyristyl phosphate	0.5 g, moistened with water	3 male NZW rabbits	4 h semi-occlusive patch	not irritating; no erythema or edema	29
dimyristyl phosphate	12.5-75% in distilled water; 0.2 ml	3 female guinea pigs	0.1 ml injections of 25% FCA, 50% FCA, or distilled water were administered after a 1-wk non-treatment period, 24-h occlusive patches were applied; the sites were scored at 48 and 72 h	no reactions were observed at any dose	30
dimyristyl phosphate	75% in distilled water	female guinea pigs; 10 test animals, 5 controls	guinea pig maximization test - intradermal induction: 50% aq. FCA, 12.5% aq. dimyristyl phosphate, or solution of 12.5% dimyristyl phosphate + 50% aq. FCA - 0.5 ml 10% SLS was painted on skin 24 h prior to epidermal induction, which consisted of a 48 h occlusive patch, 0.5 ml, with 75% test article - challenge, 11 days after induction: 24 h occlusive patch, 0.5 ml	not an irritant or sensitizer	30
HUMAN					
C20-22 alkyl phosphate	5% in an emulsion (emulsion not defined)	49 subjects	HRIPT induction: three 48- or 72-h occlusive patches (Finn chambers) with 20 µl of test material were applied per wk for 3 wks; test sites were scored 30 min after patch removal challenge: after a 2-wk non-treatment period, a 48-h patch was applied to a previously untreated site; the test site was scored 24 and 48 h after patch removal	not an irritant or a sensitizer - the mean irritation index was 0.08 during induction and 0.06 at challenge - the GII was 0.08	20
hair cream containing 1.0% dicetyl phosphate	undiluted; 0.2 g	108 subjects	HRIPT induction: nine 2 cm^2 patches were each applied for 24 h during induction (i.e., 3x/wk for 3 wks), and the test sites were scored at 48- or 72-h challenge: after a 10-15 day non-treatment period, 24-h patches were applied to a previously untreated site; the test sites were scored 48 and 72 h after application	not a sensitizer - no adverse event were reported	31

Abbreviations: DMF – dimethylformamide; DNCB – dinitrochlorobenzene; FCA - Freund's complete adjuvant; GII – global irritation index; GPMT – guinea pig maximization test; HRIPT – human repeated insult patch test; LLNA – local lymph node assay; NZW – New Zealand White; SLS – sodium lauryl sulfate

Table 10. Ocular irritation studies

Test Article	Concentration/Dose	Test System	Method	Results	Reference
			ALTERNATIVE STUDIES		
potassium cetyl phosphate	3% solution diluted by 50% with distilled water	CAM	HET-CAM 0.3 ml was applied to the four CAMs; the CAM was rinsed after 20 sec observations were made after 30 sec, 2 min and 5 min	practically no ocular irritation potential - average score of 1.75/32	34
potassium lauryl phosphate	10% solution diluted by 50% with distilled water		HET-CAM - procedure same as above	moderate ocular irritation potential - average score of 12/32	32
oleyl phosphate	applied neat	isolated chicken eyes	*in vitro* eye corrosives and severe irritants study - performed according to OECD Guideline 438	demonstrated the potential to be corrosive and a severe ocular irritant - corneal opacity was 4/4, the corneal thickness score was between 0-2/2, and the fluorescein score was 3/3. The test material was applied for 10 sec	21
			NON-HUMAN STUDIES		
phosphoric acid, C16-18 alkyl esters, potassium salts	applied neat, 0.1 ml	3 NZW rabbit	instilled into the conjunctival sac of the left eye; the eyes were not rinsed; the contralateral eye served as the untreated control	not irritating - 4 of the animals had slight conjunctival redness, with one having a maximum score of 1/4; all redness was reversed by 48 or 72 h - one rabbit had a chemosis score of 1/4 at 24 h; this effect subsided by 48 h	22
potassium lauryl phosphate	77% paste; 0.1 g	3 NZW rabbits	instilled into the conjunctival sac of one eye; the eye was rinsed after 24 h	irritating - effects on the conjunctivae, iris, and cornea in all animals at 24 h, and signs of irritation were present in 2/3 animals after 7 days	19
potassium lauryl phosphate	neat; 0.05 g	3 albino Russian rabbits	as above	irritating - slight corneal opacity and signs of irritation were also observed for the conjunctivae and iris in all animals up to 24 h after rinsing; severity of the effects had decreased by 72 h after rinsing	19
C20-22 alkyl phosphate	neat, 0.1 g	3 female NZW rabbits	instilled into the conjunctival sac of the right eye; the eyes were not rinsed; the contralateral eye served as the untreated control	moderately irritating - the max. overall irritation score was 21.3 on day 1 - slight to moderate conjunctival reactions observed 1 h after instillation were totally reversible by day 7 and 8 - slight to moderate corneal reaction noted in 2 animals at 24 h was totally reversible by days 4-6	20
dicetyl phosphate	20% suspension in distilled water, 0.035 g	6 male NZW rabbits	as above	slightly irritating - global average (24 h +48 h + 72 h readings: conjunctiva, chemosis – 0.55, enathema – 0.0; iris, congestion – 0.83; corneal opacity – 0	33
dimyristyl phosphate	neat, 0.1 g	3 male NZW rabbits	as above	non-irritating -conjunctival irritation was observed in all animals at 1 h; reversible in 2 animals with 48 h - congestion of the iris in one animal at 1 h; reversible in <24 h - corneal opacity in 1 animal at 24 h, clear by 48 h - all eyes were clear by day 5	35

Abbreviations: HET-CAM – hen's egg test utilizing the chorioallantoic membrane; NZW – New Zealand White

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C9-15 ALKYL PHOSPHATE	07C - Foundations	3
C9-15 ALKYL PHOSPHATE	10A - Bath Soaps and Detergents	1
C9-15 ALKYL PHOSPHATE	12A - Cleansing	4
C9-15 ALKYL PHOSPHATE	12D - Body and Hand (exc shave)	1
C9-15 ALKYL PHOSPHATE	12F - Moisturizing	4
C20-22 ALKYL PHOSPHATE	03G - Other Eye Makeup Preparations	2
C20-22 ALKYL PHOSPHATE	07C - Foundations	1
C20-22 ALKYL PHOSPHATE	11G - Other Shaving Preparation Products	1
C20-22 ALKYL PHOSPHATE	12C - Face and Neck (exc shave)	3
C20-22 ALKYL PHOSPHATE	12F - Moisturizing	3
C20-22 ALKYL PHOSPHATE	13B - Indoor Tanning Preparations	4
CASTOR OIL PHOSPHATE	03C - Eye Shadow	1
CASTOR OIL PHOSPHATE	12F - Moisturizing	1
CETYL PHOSPHATE	03D - Eye Lotion	2
CETYL PHOSPHATE	03F - Mascara	1
CETYL PHOSPHATE	03G - Other Eye Makeup Preparations	4
CETYL PHOSPHATE	04E - Other Fragrance Preparation	1
CETYL PHOSPHATE	07C - Foundations	1
CETYL PHOSPHATE	11A - Aftershave Lotion	1
CETYL PHOSPHATE	11E - Shaving Cream	1
CETYL PHOSPHATE	12A - Cleansing	3
CETYL PHOSPHATE	12C - Face and Neck (exc shave)	12
CETYL PHOSPHATE	12D - Body and Hand (exc shave)	34
CETYL PHOSPHATE	12E - Foot Powders and Sprays	1
CETYL PHOSPHATE	12F - Moisturizing	18
CETYL PHOSPHATE	12G - Night	6
CETYL PHOSPHATE	12H - Paste Masks (mud packs)	5
CETYL PHOSPHATE	12J - Other Skin Care Preps	2
CETYL PHOSPHATE	13B - Indoor Tanning Preparations	1
CETYL PHOSPHATE	13C - Other Suntan Preparations	1
DICETYL PHOSPHATE	03D - Eye Lotion	1
DICETYL PHOSPHATE	03F - Mascara	7
DICETYL PHOSPHATE	05A - Hair Conditioner	5
DICETYL PHOSPHATE	05B - Hair Spray (aerosol fixatives)	1
DICETYL PHOSPHATE	05C - Hair Straighteners	8
DICETYL PHOSPHATE	05G - Tonics, Dressings, and Other Hair Grooming A	6
DICETYL PHOSPHATE	05I - Other Hair Preparations	9
DICETYL PHOSPHATE	06A - Hair Dyes and Colors (all types requiring cauti	40
DICETYL PHOSPHATE	06F - Hair Lighteners with Color	1
DICETYL PHOSPHATE	07I - Other Makeup Preparations	1
DICETYL PHOSPHATE	12C - Face and Neck (exc shave)	6
DICETYL PHOSPHATE	12D - Body and Hand (exc shave)	8
DICETYL PHOSPHATE	12F - Moisturizing	8
DICETYL PHOSPHATE	12G - Night	4
DICETYL PHOSPHATE	12H - Paste Masks (mud packs)	3
DICETYL PHOSPHATE	13A - Suntan Gels, Creams, and Liquids	1
DIOLEYL PHOSPHATE	06B - Hair Tints	1
LAURYL PHOSPHATE	12A - Cleansing	2
POTASSIUM C12-13 ALKYL PH	12J - Other Skin Care Preps	2

POTASSIUM CETYL PHOSPH/	01B - Baby Lotions, Oils, Powders, and Creams	5
POTASSIUM CETYL PHOSPH/	02A - Bath Oils, Tablets, and Salts	4
POTASSIUM CETYL PHOSPH/	03D - Eye Lotion	10
POTASSIUM CETYL PHOSPH/	03E - Eye Makeup Remover	1
POTASSIUM CETYL PHOSPH/	03F - Mascara	45
POTASSIUM CETYL PHOSPH/	03G - Other Eye Makeup Preparations	10
POTASSIUM CETYL PHOSPH/	04E - Other Fragrance Preparation	1
POTASSIUM CETYL PHOSPH/	07B - Face Powders	1
POTASSIUM CETYL PHOSPH/	07C - Foundations	5
POTASSIUM CETYL PHOSPH/	07F - Makeup Bases	2
POTASSIUM CETYL PHOSPH/	07G - Rouges	1
POTASSIUM CETYL PHOSPH/	07I - Other Makeup Preparations	5
POTASSIUM CETYL PHOSPH/	08C - Nail Creams and Lotions	1
POTASSIUM CETYL PHOSPH/	10E - Other Personal Cleanliness Products	3
POTASSIUM CETYL PHOSPH/	11E - Shaving Cream	1
POTASSIUM CETYL PHOSPH/	12A - Cleansing	17
POTASSIUM CETYL PHOSPH/	12C - Face and Neck (exc shave)	52
POTASSIUM CETYL PHOSPH/	12D - Body and Hand (exc shave)	44
POTASSIUM CETYL PHOSPH/	12F - Moisturizing	98
POTASSIUM CETYL PHOSPH/	12G - Night	21
POTASSIUM CETYL PHOSPH/	12H - Paste Masks (mud packs)	8
POTASSIUM CETYL PHOSPH/	12I - Skin Fresheners	1
POTASSIUM CETYL PHOSPH/	12J - Other Skin Care Preps	29
POTASSIUM CETYL PHOSPH/	13A - Suntan Gels, Creams, and Liquids	3
POTASSIUM CETYL PHOSPH/	13B - Indoor Tanning Preparations	7
POTASSIUM LAURYL PHOSPH	12A - Cleansing	1
POTASSIUM LAURYL PHOSPH	12C - Face and Neck (exc shave)	3
STEARYL PHOSPHATE	03B - Eyeliner	1
TRIOLEYL PHOSPHATE	07E - Lipstick	3

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: July 30, 2014

SUBJECT: Summary of French Study on Dimyristyl Phosphate

EviC-CEBA. 1997. Summary of Evaluation du potentiel sensibilisant cutané de la substance Dimyristyl Phosphate. (complete study in French provided to CIR May 19, 2014)

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Summary:
EviC-CEBA. 1997. Evaluation du potentiel sensibilisant cutané de la substance Dimyristyl Phosphate. (complete study in French provided to CIR May 19, 2014)

Test Material: Dimyristyl Phosphate

Procedure: Guinea pig maximization test according to OECD guideline 406

Determination of the Maximal Non-Irritating Concentration:

- Three Female Guinea Pigs
- Three 0.1 ml Intradermal injections each:
  - 50% Freunds Complete Adjuvant (FCA) in distilled water
  - Distilled Water
  - 25% FCA in distilled water
- Following a 7-day rest, occluded patches containing 0.2 ml of the following were applied for 24-hours:
  - 75% Dimyristyl Phosphate
  - 50% Dimyristyl Phosphate
  - 25% Dimyristyl Phosphate
  - 12.5% Dimyristyl Phosphate
- Evaluation of the Test Sites 24 and 48-hours after patch removal
- No Reactions were noted on any test site – 75% and 50% were chosen as the maximal concentrations for the Sensitization Determination.

Determination of the Intradermal Concentration:

- Two female guinea pigs were given 0.1 ml intradermal injections of Dimyristyl Phosphate at 50, 25, 12.5, and 6.25%. 12.5% was determined to be the proper intradermal dose based on irritation scores of 2.

Determination of the Sensitization Potential:

- Induction

  Intradermal injections
  - Control Group – 5 female guinea pigs
    - Distilled Water
    - 50% FCA in distilled water
    - 25 % FCA in distilled water
  - Treatment Group – 10 female guinea pigs
    - 50% FCA in Distilled Water
    - 12.5% Dimyristyl Phosphate in Distilled water
    - 12.5% Dimyristyl Phosphate in 50% FCA in Distilled Water

  Topical Induction

  Because the test material was not an irritant, a 10% SLS solution (0.5 ml) was applied 24 hours prior to a 0.5 ml dermal application of 75% Dimyristyl Phosphate (48 hour occlusive patch). Controls were treated with 0.5 ml distilled water.
- Challenge – 11-days post induction:
  - Control Group – Distilled Water, occluded for 24 hours.

    - Treatment Group – 0.2 ml 75 and 50% Dimyristyl Phosphate in distilled water for 24-hours (both control and treated guinea pigs were examined at 24 and 48 hours)
- Results – none of the Control or Treated sites showed signs of irritation or sensitization.

Conclusion: Dimyristyl Phosphate does not induce dermal sensitization in the guinea pig maximization test.

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Memorandum

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

FROM: Jay Ansell, Ph.D., D.A.B.T.
Industry Liaison to the CIR Expert Panel

DATE: June 3, 2014

SUBJECT: Comments on the Draft Report Prepared for the June 2014 CIR Expert Panel Meeting: Safety Assessment of Alkyl Phosphates as Used in Cosmetics

Please note that there is also a NICNAS assessment (link available from the On-Line) on C20-22 Alkyl Phosphate. Although there are no additional safety studies compared to what is presented on the ECHA website, there is some information on how the material is sold to the industry and information on impurities, e.g., <1% phosphoric acid.

Ocular Irritation - Please include the concentration of Potassium Lauryl Phosphate that was an irritant in rabbit eyes, and the concentrations C20-22 Alkyl Phosphate and Dicetyl Phosphate that were irritating.

Irritation and Sensitization - At what concentration was Potassium Lauryl Phosphate negative in a guinea pig maximization test?

At what concentration was Oleyl Phosphate negative in alternative dermal irritation assays?

Table 6 - Please indicate whether or not reproductive organs were examined in the 90-day study on Potassium C9-15 Alkyl Phosphate.

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Memorandum

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

FROM: Jay Ansell, Ph.D., D.A.B.T.
Industry Liaison to the CIR Expert Panel

DATE: July 8, 2014

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

In the Introduction, please provide some indication of the carbon chain length of the alkyl groups of the compounds in this report, e.g., with at least one alkyl group with a carbon chain length of 8 carbons or more, while one alkyl group can be as small as 2 carbons.

Non-cosmetic - For what material may "niosomes" serve as a deliver system? For which route of exposure are "niosomes" used as a delivery system?

Singe Dose Exposure - How long was the exposure in the inhalation study?

Reproductive and Developmental Toxicity - Please include the gestation days of exposure in the text.

Genotoxicity - Rather than stating that "these ingredients do not appear to be gentoxic", it would be more accurate to state that the results of all of the assays were negative.

Table 1 - Rather than showing Figure 1 multiple times in this table, please change the added text to state "R, R', and R'' of Figure 1 may be...."

Table 2 - Please use soy or soybean oil rather than soja oil throughout this table.

The solubility of Lauryl Phosphate, Oleyl Phosphate and Stearyl Phosphate is not clear as it states "in paraffin, soja oil, or isopropyl palmitate at room temperature; not soluble at room temperature". Are these ingredients soluble in the three named solvents at room temperature?

Table 3 - C9-15 Alkyl Phosphate: The Council use survey included a concentration of 0.0044% in bath soaps and detergents. This concentration is not currently shown in the Mucous Membrane row.

Cetyl Phosphate: What is the source of the 2% concentration in the Spray row? The Council survey reported use at 2% in eye lotion, body and hand products (not spray) and

suntan products (not spray). No other 2% concentrations were included in the results of the survey.

Table 6 - Please indicate whether or not reproductive organs were examined in the 90-day study of Potassium C9-15 Alkyl Phosphate.

NOEL needs to be added to the list of abbreviations at the bottom of the table (the definition is present, but the acronym is missing).

Table 9, last Potassium Lauryl Phosphate study - It appears that "without" [metabolic activation] is missing after "≤1000 μg/ml".

Table 10 - last Oleyl Phosphate study - Please correct: "in in DMF"

first Dicetyl Phosphate study - Please correct: "as a paste is 0.575 g olive oil"