Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	February 10, 2023
Panel Meeting Date:	March 6-7, 2023

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Daniel C. Liebler, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi Raj, Senior Scientific Analyst/Writer, CIR.

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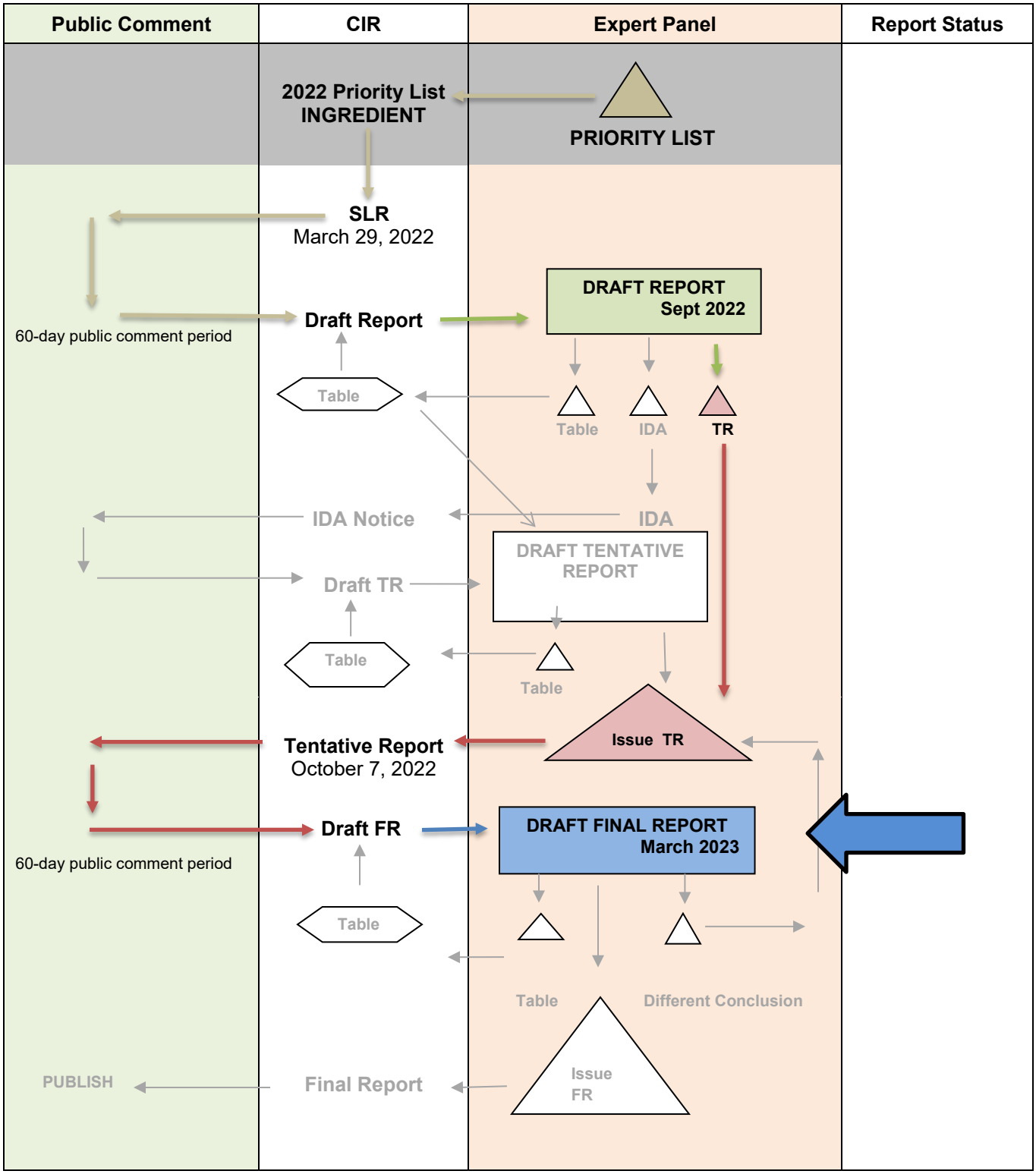
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Polyhydroxystearic Acid

MEETING March 2023



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc.
Senior Scientific Analyst/Writer, CIR
Date: February 10, 2023
Subject: Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as Used in Cosmetics (identified as *report_PolyhydroxystearicAcid_032023* in the pdf). This is the second time the Expert Panel for Cosmetic Ingredient Safety (Panel) is seeing a safety assessment of these 3 cosmetic ingredients. At the September 2022 meeting, the Panel issued a Tentative Report for public comment with the conclusion that Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use is presented both cumulatively by likely duration and exposure and individually by product category.

Comments on the Tentative Report that were received from the Council have been addressed, and follow this memo (*PCPCcomments_PolyhydroxystearicAcid_032023*). A comments response checklist is also included (*response-PCPCcomments_PolyhydroxystearicAcid_032023*).

Also included in this package, for your review, are:

- a flow chart (*flow_PolyhydroxystearicAcid_032023*)
- literature search strategy (*search_PolyhydroxystearicAcid_032023*)
- data profile (*dataprofile_PolyhydroxystearicAcid_032023*)
- transcripts from the previous meeting (*transcripts_PolyhydroxystearicAcid_032023*)
- report history (*history_PolyhydroxystearicAcid_032023*)

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: October 20, 2022

SUBJECT: Tentative Report: Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as Used in Cosmetics (release date: October 7, 2022)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as Used in Cosmetics.

Method of Manufacture – What happened to the 350 l and the 650 l capacity bioreactors? If they have nothing to do with the manufacture of Poly(3-Hydroxyoctanoic Acid), there is no need to mention them.

Non-Cosmetic – American Society for Testing [and] Materials should be deleted as the current name is ASTM International. Although they continue to use ASTM, they no long use "American Society for Testing and Materials" (other than listing it as a former name).

Toxicokinetics; Summary – If reference 33 did not find the radioactivity from implanted [^{14}C]Polylactic Acid in the feces, urine, major organs or implant chamber (stated only in the summary), where did the radioactivity go? Did they look for the radioactivity in expired air? Did they indicate the total amount of the implanted radioactivity that was recovered?

Genotoxicity – Assuming that "0, 50, 200 or 200 ml/kg" is ml/kg body weight, these values should be called "doses" rather than "concentrations".

Discussion – The Expert Panel indicated that the "connectivities" were the same among these three polymers. The physical forms are different, e.g., Polyhydroxystearic Acid can be a liquid while Polylactic Acid is a solid.

Dermal Irritation and Sensitization; Table 6 – Please indicate that saline was used to make the extracts of Polylactic Acid film that were tested.

Polyhydroxystearic Acid - March 6-7, 2023 Panel Meeting – Preethi Raj			
Comment Submitter: Personal Care Products Council **Date of Submission: October 20, 2022 (comments received on Tentative Report after October 7, 2022 posting)**			
#	**Report section/Comment**	**Response/Action**	**Needs Panel Input**
1	Method of manufacture- do not need to mention 350 l and 650 l capacity bioreactors if they are not involved in the manufacture process	- revised, removed 350 l	
2	Non-Cosmetic – correct name of ASTM International	- corrected	
3	Toxicokinetics; Summary -	- addressed	
4	Genotoxicity – if units of exposure are ml/kg, should be changed to does rather than concentrations	- revised	
5	Discussion- The Panel had indicated that the “connectivities” between the 3 polymers was the same	- revised	
6	Dermal Irritation and Sensitization- Table 6 – indicate that saline was used to make the Polylactic Acid extracts	- added	

CIR History of:

Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid

July 2021

-Concentration of use data submitted by Council

January 2022

-FDA frequency of use data obtained

March 2022; April 2022

- SLR posted on the CIR website; received SLR comments

Data received, by date:

April 11, 2022:
Polyhydroxystearic Acid
- Chemistry and molecular weight data
- 100% Polyhydroxystearic Acid; HRIPT in 50 subjects

April 15, 2022:
- Marzulli-Maibach HRIPT; product containing 4% Polylactic Acid (104 subjects)
- Modified Marzulli-Maibach HRIPT; product containing 3.45% Polyhydroxystearic Acid (107 subjects)

September 2022

A Draft Report was presented to the Panel. The Panel discussed that these are large molecules, which are not likely to be absorbed. Additionally, the Panel considered the prior safety assessments of the corresponding monomers of these ingredients, and surmised that the systemic toxicity of these polymers would not be different. The Panel was further reassured of the dermal safety of these ingredients by the US Food and Drug Administration (FDA)-approved uses of Polylactic Acid in medical devices, as well as the existing ASTM International standard for this ingredient.

Thus, the Panel issued a Tentative Report for public comment with the conclusion that these 3 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

October 2022

Comments on the Tentative Report were received from Council. No additional data was received.

March 2023

A Draft Final Report is being presented to the Panel.

Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid Data Profile* – March 6-7, 2023 – Writer, Preethi Raj																														
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Polyhydroxystearic Acid	X		X																		X			X					
Poly(3-Hydroxyoctanoic Acid)		X	X																										
Polylactic Acid	X	X	X			X									X	X				X	X			X		X			X

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

[Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid]

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Polyhydroxystearic Acid	27924-99-8 58128-22-6	NR	NR	NR	NR	✓*	NR	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	✓*
Poly(3-Hydroxyoctanoic Acid)		✓*	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓*
Polylactic acid	9051-89-2 26917-25-9 26811-96-1	✓	✓*	NR	NR	✓	NR	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	✓*

NR – not reported; ✓*- data available is not relevant to assessment

Search Strategy

[*total # of hits / # useful hits*]

PubMed (as of 01/17/2023):
((((((((((((((((((((((polyhydroxystearic acid) OR (Poly(3-Hydroxyoctanoic Acid))) OR (27924-99-8)) OR (58128-22-6)) OR (Dispersun DSP OL 100)) OR (Dispersun DSP OL 300)) OR (Octacare DSP OL100)) OR (Pelemel PHS-8)) OR (Salacos HS-6C)) OR (Polylactic acid)) OR (9051-89-2)) OR (26917-25-9)) OR (26811-96-1)) OR (polylactide)) OR (cyclic poly lactate)) OR (Ecoscrub 20 PC)) OR (Flo-Beads BF)) OR (FLO Beads-BL)) OR (Flo-Beads)) OR (BR)) OR (Lacea)) OR (PLLA-MS)) OR (Purasorb OL)) AND (toxicity) – 32,521 hits/0 new or useful

General Search

Polyhydroxystearic Acid – 4/0
Poly(3-Hydroxyoctanoic Acid) – 29/2
Polyhydroxystearic acid cosmetic toxicity – 0/0
Polylactic acid cosmetic toxicity – 15/2
Polyhydroxystearic Acid toxicity – 0/0
Poly(3-Hydroxyoctanoic Acid) toxicity – 0/0
Polylactic Acid toxicity – 6787/3
polyhydroxystearic acid cosmetic toxicity - 20,100/2
poly(3-hydroxyoctanoic) acid method of manufacture – 114,000/1
polyhydroxystearic acid dermal toxicity – 23,500/0
polyhydroxystearic acid dermal irritation and sensitization – 16,800/0
poly(3-hydroxyoctanoic acid) dermal toxicity - 96,100/0
poly(3-hydroxyoctanoic acid) dermal irritation and sensitization – 17,600/0
polylactic acid dermal toxicity - 644,000/0
polylactic acid dermal irritation and sensitization – 70,900/1

LINKS

Search Engines

- Pubmed - http://www.ncbi.nlm.nih.gov/pubmed
  - appropriate qualifiers are used as necessary
  - search results are reviewed to identify relevant documents
- Connected Papers - https://www.connectedpapers.com/

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

SEPTEMBER 2022 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – September 26, 2022

[Belsito Team minutes are being located]

Cohen Team – September 26, 2022

Dr. David Cohen - Yeah. OK. Yeah, there's very interesting. Evolution of this plant and we think there was a lot of discussion and thought about how we need to judicate grass and foods over the last couple of meetings. So I think that's great. We'll, we'll carry that motion. Next Polyhydroxystearic acid. And polylactic acid and Polyhydroxy octanoic acid. This is a draft report, so it's the first time we're seeing it and it's those three Polymeric cosmetic ingredients that we're looking at that are used as non-surfactant dispersing agent, skin conditioning agents and abrasives. We have reported use we have Maximum concentration for high polyhydroxystearic acid at 14.2% in a lipstick polylactic acid is 5%. And Polyhydroxy octanoic acid we have no reported use. The panel previously has reviewed the monomers, namely for hydroxysteroid acid in in 1999 and lactic acid, and reaffirmed in 15 lactic acid in 1998, reaffirmed in 2017. There was a comment about polylactic acid being listed in an FDA approved medical device, which was a surgical tape dressing and orthotic device in information requests. In February, regarding irritation and sensitization have not been received. A comment that I noted in 1998 lactic acid was concluded to be safe as used in cosmetic products that concentration is less than 10%. PH of greater than 3.5. And when formulated to avoid increasing sun sensitivity or when directions for use include daily use of sun protection. And that is safe and salon products that concentrations less than 30% in final formulations greater than pH of three. I'm sorry to be rambling, I've never seen a conclusion like that before. It's just, it's very specific and detailed. Just for comment, we have method of manufacturing except for hydroxysteroid acid. And we have impurities and we have highest concentration of sensitization at neat.

Dr. Wilma Bergfeld - I'm on. I'm on line this fixed.

Dr. David Cohen - But what's? What's fixed?

Dr. Wilma Bergfeld - Yeah. I know, John.

Dr. David Cohen - Oh, I think that was Wilma on a different call and we have highest concentration of need at Polyhydroxy polyhydroxystearic acid. So I'm sorry, that was a mouthful. There was a lot in this report. First, are these all similar enough? For us to read across and put them all together in this report.

Dr. David Ross - Good question. You know the read across I had a note and same class, but you know different chain lengths, different forms, liquid solids. So I don't know about read across.

Dr. Susan Tilton C - I made similar notes, especially with regard to. Polyhydroxystearic acid.

Dr. David Cohen - So does that get us to calling these what will ask for individual we're going to ask for data on each of these, but we do have some data on the monomers, right?

Dr. Tom Slaga - Right, all of monomers are safe.

Dr. David Cohen - Any comment Tom on that conclusion for lactic acid and Wilma too. I've never seen a conclusion like that before. Where it had so many provisions and so many outlines.

Dr. Tom Slaga - I know, I know.

Dr. David Cohen - It Thomas.

Dr. Wilma Bergfeld - I didn't even remember that one.

Dr. Tom Slaga - We never have done that again.

Dr. Wilma Bergfeld – Never no.

Dr. Tom Slaga - I don't think.

Dr. Wilma Bergfeld - We have a lot of problems with those fruit acids. They had some irritation that I had some photoactivation, and I suspect we were responding to that at that time and the FDA was also looking at it at that time as an OTC. So I think the circumstances were different.

Dr. David Cohen - Thomas, I'm sorry.

Thomas Gremillion (CFA) - I yeah, I just. I was wondering reading that you know what the risk are of like the that require application by trained professionals for example.

Dr. Wilma Bergfeld - Carcinogenicity was the issue.

Thomas Gremillion (CFA) - OK. Thank you.

Dr. Wilma Bergfeld - Photo activated. So it was a sun induced chemical reaction.

Dr. David Cohen - Now these are polymers, so we're dealing with a completely different set of issues, usually less problematic, not more problematic.

Dr. Tom Slaga – Right.

Dr. Wilma Bergfeld - Yeah. They're big, big polymers too.

Dr. David Ross - Yeah, but the you know the.

Dr. Tom Slaga - And we know that the monomers are safe for the majority of them are that we have data on.

Dr. David Ross - There was, you know, with the comment in here which I think is probably need to address, is that, a significant percentage 20% of the of the PHSA has molecular weight less than 1000, so they are oligomers. You know they're not the necessarily the monomers, but they're not the big polymer and so, you know, I had a if that's the case, then I think you know these things are high molecular weight, so they wouldn't be absorbed, but the but you know the ligaments might less than 1000 and not the monomers necessarily there might be, but they're not. So I had a question there because we've got no dermal tox at maximum use some PHA.

Dr. Tom Slaga - Yeah.

Dr. David Ross - So I had a question there on whether or not we needed a 20 dermal or not. So that's something to consider. On the PHSA was used in lipsticks up to 14.2% as David said, so I felt we needed at least some or tox. There's none at all in the document I could see and again there was very little ocular data provide that's used at up to 8% in ocular preps. So you know those three issues, dermal tox, a little, some oral and ocular.

Dr. Tom Slaga - You know. Yeah. That the dermal tox, I mean, this is a draft once again and the dermal tox I had is a possibility would be nice to have at least a 28 day as you mentioned.

Dr. David Cohen – For?

Dr. Susan Tilton - For PHA. And I would also add an inhalation study for PHA a given its use in hairsprays and face powder. And just again, I think we should consider it as a separate ingredient, not grouped with polylactic acid.

Dr. David Cohen – So Polyhydroxystearic acid, you, you feel is different enough to separate?

Dr. Susan Tilton - I do, I think. It's also the chemical with them or the ingredient with the most uses and different types of uses, and we that we don't have data for. But.

Dr. David Ross - I agree with that.

Dr. Susan Tilton - Structure itself is very different.

Dr. David Ross - Yeah. So I agree with separating them, but with respect to the inhalation, give me a small background on the inhalation I'm trying to (*inaudible) incidental. Contact on this one. Here we go. Right.

Dr. Susan Tilton - It's just based on its use profile and the fact that there is no data. Actually for any of these. But it is in the.

Dr. Wilma Bergfeld - You have some dermal data. Clinical human.

Dr. David Cohen - Right. But the comment was that it was being used in Hairspray with potential for inhalation.

Dr. Wilma Bergfeld - That could always be covered in a discussion.

Dr. David Ross - I think you had boilerplate in for that. Did you not?

Dr. Wilma Bergfeld - Yep.

Dr. David Cohen - So no on the inhalational.

Dr. David Ross - A Susan a yes.

Dr. David Cohen - No, no, I know. But we have to.

Dr. Susan Tilton – (*inaudible) conclusion.

Dr. David Cohen - We're presenting this tomorrow.

Dr. David Ross - Yeah.

Dr. Wilma Bergfeld - While you're moving that to the discussion or you not, or are you asking for it?

Dr. David Ross - I moved it to the discussion.

Dr. Wilma Bergfeld - Yeah.

Dr. Susan Tilton - Based on the statement that's in the report. About the likelihood of it not being respirable.

Dr. David Ross - Yeah.

Dr. Susan Tilton - Is that what we're discussing?

Dr. David Cohen - Yeah, but that, that that comes up and can be a tricky point depending on the delivery, the delivery system of which it's being used.

Dr. David Ross - You mean airbrushing versus not? We have a comment in there on airbrushing also.

Dr. David Cohen - No, I know it. Yeah. But it's not just it's a cold clean line between airbrushing and a Hairspray or pump or other devices, right? I mean, it's gosh, that's I really gray area.

Dr. David Ross - So.

Dr. David Cohen - Monice and Preethi I could use some help here with the team not feeling that Polyhydroxystearic acid is not is it doesn't seem similar enough to the others, so do we keep it in the report and then just ask for the data that we're looking for and if need be, come to a split conclusion or do is this the point to break it off?

Monice Fiume (CIR) - So I'm going to defer to see what Dan Liebler hopefully gives input tomorrow, because when we developed the priority list when the groups are made, one of the questions we ask is, are they similar enough to be grouped together so that you could have read across? Of course, both teams get to have input on that tomorrow. I think it's good to have the insight as to the discussion of what may have happened last year and why they were decided they could be together. Just as a point of fact, if it is cleaved off in those other two ingredients go by themselves, they will not be reviewed for quite a while because they don't have the frequency of use to put them on the priority list. So I guess the answer is many points, yes, this

would be the point to do it rather than drag it through. You can separate them in the report and you can do a split conclusion. It all depends on the teams. If you think the information on some of the ingredients support the others than it is very good to leave them in the report. But I would like to see what the other chemists have to say tomorrow since they have better knowledge about this than I do.

Dr. David Ross - OK.

Monice Fiume (CIR) - But this usually happens during the priority list.

Dr. David Cohen - OK. If the perfectly reasonable and am I reading the group as, we're going to go out with an IDA for 28 day dermal tox?

Dr. David Ross - Right.

Dr. David Cohen - (*inaudible) oligomers.

Dr. Wilma Bergfeld - You have a large molecule and you have dermal.

Dr. David Ross - Yeah.

Dr. Wilma Bergfeld - You have skin you have (*inaudible) you have animal and you have human.

Preethi Raj (CIR) – Yeah and Doctor Cohen, I also wanted to mention that there is an HRIPT in 50 subjects with 100% polyhydroxystearic acid too.

Dr. David Cohen - Ohh thank you for correcting that for me.

Dr. David Ross - Yeah, I think that's correct. I think I had that as OK. But my asks where the 28 day dermal some oral tox and some ocular on PHSA. And I thought the dermal tox sensitization, I thought PHA was OK. Neat it's only used at 8%. And PLA was at 4% the data that we have actually used at 5. And I have a note here. David, is that OK?

Dr. David Cohen - I think so because. Yeah, I think that's close enough and it is not something that really comes up very much.

Dr. David Ross - Correct.

Dr. David Cohen - Doesn't come up at all, actually.

Dr. David Ross - If you look at the number.

Preethi Raj (CIR) - And though we haven't received, you know, much data specific to these users, there is extensive use of polylactic acid in I think collagen dressings which are applied to the skin. So perhaps that may inform the panel's decision.

Dr. David Cohen - At what percent use?

Preethi Raj (CIR) - Ohh, we don't know that, but we are sure that they are used because of I mean we found use of them in at least two PMA uses and also 2510K applications, which we've asked data pertaining to these or any other uses with these ingredients. But so far we haven't received information.

Dr. David Cohen - And that would be very useful, because those would be occlusive. Uses of the product, right? And so that would really allow some additional information.

Preethi Raj (CIR) – The Panel may help us also help our FDA Counterparts also to perhaps get this information that would be great.

Dr. David Cohen - So the IDA so it is an IDA because so we're still requesting information we're looking for that FDA material.

Preethi Raj (CIR) - But I don't think that would necessarily cause the report to be stalled, but I mean that's up to the panel.

Dr. David Cohen - Yeah. Well, its early. We've had this conversation a lot, right? FDA.

Dr. David Ross - David, could I make one more request, sorry. You know the list, (*inaudible)
And method of manufacturing now PLA is listed for industrial press. I'd like to see the method of manufacture of sending cosmetic. Because that purity was only 80 to 90% in industrial. So it might be a cosmetic, perhaps, that I don't know the answer to that question, but it would be nice to have that information method manufactured for cosmetic. Perhaps if it's out there rather than industrial preps.

Dr. David Cohen - This is for polylactic acid?

Dr. David Ross - Yeah, yeah.

Dr. David Cohen - Yeah.

Dr. Wilma Bergfeld - In direct food additive well.

Dr. David Ross - Yeah. And then just one final question from the what do we do the third compound? It's no uses the Poly, three hydroxy octanoic acid. I mean, that's the tag along with this as well. Or how does that work?

Dr. David Cohen - Well, that's the discussion about the read across. Susan, any comments on that?
Which one does that look like the most?

Dr. Susan Tilton C - I mean, I would feel more comfortable grouping that with PLA.

Dr. David Cohen - OK. So I just want to have clarity when I go out tomorrow. We're going to come out with an IDA on this, right?

Dr. Tom Slaga - Correct.

Dr. David Cohen - And we're asking for method of manufacturing of polylactic acid for cosmetic use and I just want to confirm that that is something we still want. It says industrial production of lactic acid.
The precursor for is mostly achieved so, I don't know if this pertains to polylactic acid in anyway. David, we still on, are we still requiring that?

Dr. David Ross - Looks like that's the stuff.

Preethi Raj (CIR) - Well, it does refer to the polymerization process.

Dr. David Cohen - You mean the industrial of the precursor?

Preethi Raj (CIR) - Yes, I believe so. I'm just reading here. Produce via polymerization of commercial lactic acid and lactide.

Dr. David Ross - That's so (*inaudible).

Dr. David Cohen - So we want method of manufacturing for the cosmetic use, if it's any different or not?

Dr. David Ross - Yeah, we could ask for clarification.

Dr. David Cohen - OK. And whereas.

Dr. Susan Tilton C - There's not a method of manufacturing provided for PHA. Is that correct?

Dr. David Cohen - Yes. And so we want method of manufacturing for PHA.

Dr. David Ross - Right.

Dr. David Cohen - So that's important. Thank you.

Dr. David Ross - Again, cosmetic (*inaudible). There's some drastically, but let's get it right.

Dr. David Cohen - Case for that's our main one right now. And then we're asking for the information on the FDA uses of polylactic acid. I think those were the two IDA asks that I miss any because we're going to ask the Belsito team to comment on the read across.

Dr. David Ross - But we needed 28 day dermal tox. Did you get all of that?

Dr. David Cohen - And. Yes. So that I do have the 28 day dermal tox and I wasn't sure if the conversation with Wilma had changed that at all.

Dr. David Ross - I'd still like that. I still think we need some oral thoughts.

Dr. Susan Tilton C - And you said, yeah, we discussed oral and ocular based on use for PHA.

Dr. David Cohen - For PHSA we, because they're oligomers of less than 1000 Daltons, we want 28 day dermal toxic ocular tox and we're not going to ask for inhalational tox.

Dr. David Ross - Right. We need, we need some oral tox, data to use the 14% or so and lipsticks and there's no oral talks that are in this document at all.

Dr. David Cohen - OK, so we need oral tox.

Dr. David Ross - Far as I can see, checking.

Dr. David Cohen - Cool. OK, hold on. Let me just make sure I have that all because that's it’s a big list.
Tom. Any thoughts on the tox ask?

Dr. Tom Slaga - Wait a minute. No, I don't have any additional.

Dr. David Cohen - Oral at dermal and ocular.

Dr. Wilma Bergfeld - Well, if you're going out for IDA, you should just ask for inhalation, see what's out there.

Dr. Tom Slaga - Yeah.

Dr. David Cohen - OK, I'm including it. I just. If they take careful notes here because, this evening, when you're trying to put it all together and remember what everyone asked for, it's not so easy.

Dr. Tom Slaga - Yeah.

Dr. David Cohen - OK. OK, so are we good with that Preethi do you think we have our thoughts organized enough here on this one?

Preethi Raj (CIR) - Yes, I think so. Doctor Cohen. So just to reiterate, the main asks are for method of manufacturing for polylactic acid and polyhydroxystearic acid specific to cosmetic use. I know you mentioned you would like info from the FDA for biomedical uses for polylactic acid and you're also asking for 28 day dermal tox, oral tox, inhalation tox and ocular tox for polyhydroxystearic acid.

Dr. David Cohen - Yeah. Yep, that's what I have. Perfect. Thank you.

Preethi Raj (CIR) - Thank you.

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Dr. David Cohen - OK, so this is the first time we're reviewing. Polyhydroxystearic acid, polyhydroxy, octanoic acid, and polylactic acid. These are used as non-surfactant (*inaudible) dispersing agent, skin conditioning agents and abrasives. Now we have reported use for Polyhydroxy stearic acid and polylactic acid, but no use reported for Polyhydroxystearic acid. We

have Polyhydroxystearic acid at maximum use of 14.2% in lipsticks and polylactic acid is 5% in skin cleansing products. We had a long discussion about this one as well and we issued an IDA. There was a comment about polylactic acid being listed as an ingredient in an FDA approved medical device which was addressing or orthotic device, and we wanted the concentration of use and the associated toxicology data from that FDA approval package, a method of manufacturing for Polyhydroxy stearic acid. And since PHA oligomers were could be less than 1000 daltons, we were asking for oral, dermal and ocular tox on it. And lastly, we would really want the counsel of a Don's team on whether this grouping is sufficiently related to read across. There was a discussion on our team about Polyhydroxystearic acid. Perhaps not being a structurally related to the others, and whether they belong, whether it belongs in this report should be split off. So I'll lot there to review.

Dr. Don Belsito - OK. Well, let's address your last question 1st and I'll turn it over to Dan and Allan about the grouping.

Dr. Daniel Liebler - When I looked at it I when I looked at the ingredients, particularly looking at table one, for example PDF 17. I saw essentially the, linkages between the pieces as being identical and then the difference is the length of the chain in between or the present? Well they all have branching and they have a, you know, a longer chain for the polyhydroxystearic. So, I didn't have a concern about grouping these together because you know we reviewed many ingredients where there's a sort of a relatively shorter extreme and a longer extreme. And this was not out of my comfort zone. So that's that was how I never even considered whether they didn't go together. But Allan, would you like to comment?

Dr. Allan Rettie - Like I didn't notice the vast differences in, you know, maybe the average or range of molecular weights, but again, I focused on the you mentioned that the chemical languages and that didn't give me pause because I agree with you that there was are all pretty similar.

Dr. David Cohen - And Dave and Susan, could you?

Dr. David Ross - Wait, I was waiting for Susan there. Go ahead, Susan.

Dr. Susan Tilton - I so appreciate the feedback from Don's team. I think some of the discussion we had was so I could see that these are grouped together. We were asking questions about read across and whether we could apply data from polylactic acid to PHSA cause there was a lot less dated for that group and some of the concerns I had were just about exposure and things like absorption and differences between the chemicals or between these ingredients and whether or not we would be able to make those interpretations from the other data set or and so that impacted the type of data that we wanted to collect or request on PHSA in particularly related to 28 day oral studies and ocular based on the formulation and expected use for PHSA.

Dr. David Ross - I just might add to that, I think one thing that got my attention, I appreciate Dan's and Allan comments on the similarities. I agree with that actually Dan and but you know one thing with the reader across which is tricky is a very different forms of these things. And you know, I think PHS is coming in as a viscous liquid and PLA is a stiff, glassy material. So that that was also something that got our attention.

Dr. Daniel Liebler - Yeah, the, I mean, it's a good point. The Polylactic lists of molecular weight range like 30 to 80,000. So big, big, big, you know, no, no absorption at all. And then the polyhy**drox**y stearic, which looks like an oil is coming in at minimum of thousand 1200 or 1200 I think and ranging upward in the in Table 2 to 8200, so practically speaking, not absorbed either, but you know smaller molecule. But still I think marginal if any absorption.

Dr. Don Belsito - The question right now is read across. We can get too absorption and the moment is it chemically, can we? Where are we with the read across? Because David's Group is saying that we can't, and Allan and Dan said we can. So are we kicking an ingredient out of here or are we keeping them all together?

Dr. David Cohen - It sounds like we maybe keeping them together.

Dr. Allan Rettie - Well, yeah.

Dr. Tom Slaga - Yeah, I too believe you can read across.

Dr. Don Belsito - OK, so then I will follow up.

Dr. Daniel Liebler - So can I? Can I just interject Don? I think that to two different issues, keeping them together in the same report based on chemical homology and similarity of use, that makes sense. And then the question about whether we take Polylactic data and read across to Polyhydroxystearic that's a separate issue. We may or may not want to do that and we may or may not need to do that, but I you know, I think it's I think we kind of all agree they can go together in the report but then how we use the data from one to support an endpoint evaluation from another is maybe not settled at this point.

Dr. Don Belsito - So David, we had a very different conclusion. We felt that they were safe as used despite the lack of toxin dark data. First of all, given their size, they wouldn't be absorbed. And we've also already reviewed the monomers that would be present and found them to be safe as used. We also felt that there has to be data out there given the fact that there's FDA and a ATSM approval, but we were told by Preethi that it could take years for us to get that, that the request was put in and we didn't really feel we needed to wait years for that data again. Given the fact that we've already ruled on the safety of the monomers as used in cosmetic products at levels, that would be much higher than might be present in these polymers.

Dr. David Cohen - Yeah, Don, I'm being honest. I'm not surprised by that finding because we toiled around with it as well. The monomer, the lactic acid report had a very complex conclusion to it that is rather old, but all these parameters are about concentration and pH that we would never use today. So we recognize that. We had, we were not sure if the method of manufacturing per for PHSA really was the same for the industrial use and the cosmetic use and we have had IDA's like that before. If the material is going to take that long, I don't think we need to wait for it either. We are, moved and comforted by the monomer reviews in the past. The question is the other tox data.

Dr. Don Belsito - Or we again they it's not going to be absorbed. So what tox data are you looking for other than monomer absorption and we've already looked at the monomers at higher concentrations as single ingredients.

Dr. David Cohen - Yeah. Some of the old timers of PHA are smaller, but you're right about the monomers. So let me throw it back to the team. If we might amend our motion?

Dr. Don Belsito - What would you expect the toxicity of a polymer to be different than the monomer?

Dr. David Ross - But if it doesn't get in. Right.

Dr. Don Belsito - Right.

Dr. David Ross - Which is what you're saying. I think the only issue Don was for us was these ligaments which were somewhere in between the monomer and the polymer. And then, but I think if you've got non irritating when tested, (*inaudible) and humans. You know, we talk about this quite a bit, whether or not you need to dermal tox, maybe you don't. Because you've already got that you've non irritating data there. The major issue for me I thought was there was no toxicology studies of any kind, but this with this material, dermal oral, acute oral repeated dose. And so I went for some oral tox needed in that discussion.

Dr. Wilma Bergfeld – Susan.

Dr. Susan Tilton - So it, but it sounds like the monomers themselves have been evaluated fairly extensively and at higher concentrations than what's presented here. And so I would, based on that data, I would be in support of moving forward with safe as used conclusion.

Dr. Tom Slaga - I agree with that comment. I think the monomer data supports that we can go safe as used.

Dr. David Cohen - We had a number of e-mail exchanges about this as well. What about the method of manufacturing for PHSA? David, what was what are your what are your thoughts on that? Because this is still early and we can, we can ask for the method of manufacturing data if we need it.

Dr. David Ross - I think the main issue with the method of manufacture was that not the LA which was which was commercial grade and (*inaudible).

Dr. David Cohen - Yes.

Dr. Allan Rettie - Was that the one where there was up to 20% impurities identified probably as the oligomers?

Dr. David Ross - I think that was.

Dr. Don Belsito - Yes.

Dr. Wilma Bergfeld - Yeah.

Dr. David Ross - Feels that say yeah.

Dr. Daniel Liebler - Yep.

Dr. Allan Rettie - The oligomers, you know would multiple units would be over a molecular weight of 1000. So we'd still be enough. In an area where there wouldn't be much, if any, dermal absorption. So is that a concern?

Dr. David Cohen - So Allan, based on method of manufacturing, you'd expect those impurities to be the oligomers?

Dr. Allan Rettie - I don't know. I was. I was just surmising that that, that might be what they were. But it's not. It's not documented. PHA is got a weight average molecular weight listed, but no number average. And I wasn't quite sure how relevant that was. So, I agree. We're early in the game and we could ask for this.

Dr. Don Belsito - Yeah.

Dr. Daniel Liebler - I think you might. Consider this as Dave just pointed out. So, the on PDF 13 under impurities, the first entries of polyhydroxy stearic and it says according to a supplier, 20% of the molecular weight of polyhydroxy stearic acid is less than 1000. Which is attributable, to oligomers. I think you can keep under 1000 if you get up in the dimer trimmer range with these. So those are oligomers. But again, you're back to the issue of our is that really of concern, it sounds like that's the impurity and it gets us back to the argument about well the monomers are safe. You know the dimer trimers their main brought

of any transformation is probably going to be hy**drol**ysis back to the monomeric components. So, I think that you kind of land back in the safe bucket there. Anyway, that's how I read that and thought about it.

Dr. David Cohen - Thank you guys that, that that's really helpful. Team, I'm going to amend our motion if this, let me know if there's any objections.

Dr. Tom Slaga - No objections.

Dr. David Ross - I can go with that. I'm just one question for you the teams chemist. Did you have any comments on the polylactic acid on impurities down on that same page? And again, that was commercial description of the commercial synthesis rather than the cosmetic grade synthesis.

Dr. Daniel Liebler - Yeah, I mean, we've again, this is something I've sort of absorbed over the years, no pun intended that, that there really isn't a distinction between commercial and cosmetic grade for many ingredients, particularly things like this. So you know it can be either DL or DL for the lactic, any impurities are leftover lactic and then they list a few. You know things they look for like are arsenic and iron and such. So I didn't have a concern about that, but I don't think there's a, I mean, I could be industry could be asked if there's if this represents what's actually used in cosmetics. We usually don't get a satisfactory answer to that question. But they're usually isn't a good reason for them to make it more than one way, particularly based on, you know, what the uses are. If it's in a medical device and then some of its use in cosmetic and some of its use in food stuff.

Dr. Wilma Bergfeld - So are we back to David to restating his motion and having it second? Your amended motion.

Dr. David Cohen - Yes. My amended motion is that polyhydroxy stearic acid. Polly hydroxy octanoic acid and polylactic acid are safe as used in current practices and concentrations in this assessment.

Dr. Don Belsito – 2nd.

Dr. Wilma Bergfeld - 2nd and any further comment that we need to make here or, just discussion points that we need? Specifically to the.

Dr. Don Belsito - I think we've already done all that.

Dr. Paul Snyder - Well, no, Don, we had the, there was a vegetable source. So you we were questioning whether we need the botanical?

Dr. Don Belsito - Bart, I yeah, I mentioned that that there was a potential vegetable source and Bart said we didn't add the botanical boilerplate when it was a purified chemical.

Dr. Bart Heldreth - Right, once there's an essentially enough processing that that we wouldn't presume that there would be any say something like metals leftover then we don't bother with that boilerplate.

Dr. Wilma Bergfeld - How about the method of manufacturing? Any comment to be made in that in the discussion?

Dr. Don Belsito - No.

Dr. Wilma Bergfeld - No. Please.

Preethi Raj (CIR) - May I verify the discussion points Doctor Bergfeld with the panel?

Dr. Wilma Bergfeld - Please.

Preethi Raj (CIR) - So we're going to mention these are large polymers not likely to be absorbed. They're the monomers, are clear to safe. There is FDA approved use and ASTM status also including the respiratory boilerplate with airbrush caveat with the panel like to add anything else since with the absence of tox data in this report?

Dr. Don Belsito - I think the fact that the monomers are clear and that they're large molecules that wouldn't be absorbed clear as the absence of tox dark data.

Preethi Raj (CIR) - OK. Thank you.

Dr. David Cohen – Reference back to the original monomer reports.

Preethi Raj (CIR) - OK. Thank you.

Safety Assessment of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as Used in Cosmetics

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ABBREVIATIONS

CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
DNFB	dinitrofluorobenzene
EFSA	European Food Safety Authority
FDA	Food and Drug Administration
HET-CAM	hen's egg-chorioallantoic membrane
HRIPT	human repeated insult patch test
MII	mean irritation index
MW	molecular weight
NR	none reported
Panel	Expert Panel for Cosmetic Ingredient Safety
PII	primary irritation index
RPMI	Roswell Park Memorial Institute
US	United States
VCRP	Voluntary Cosmetic Registration Program
wINCI; *Dictionary*	web-based *International Cosmetic Ingredient Dictionary and Handbook*

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as used in cosmetic formulations. These ingredients are reported to function in cosmetics as a non-surfactant dispersing agent, a skin-conditioning agent, and an abrasive agent, respectively. The Panel reviewed the available data to determine the safety of these ingredients and concluded that these ingredients are safe in cosmetics in the present practices of use and concentrations described in this safety assessment.

INTRODUCTION

This assessment reviews the safety of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), these ingredients are reported to function in cosmetics as a non-surfactant dispersing agent, a skin-conditioning agent, and an abrasive, respectively (Table 1).[1]

These 3 ingredients each comprise a polymer synthesized from hydroxycarboxylic acid monomers. These monomers vary only in alkyl chain-length and position of the hydroxy substitution. The Expert Panel for Cosmetic Ingredient Safety (Panel) has previously reviewed the safety of two of the monomers, hydroxystearic acid and lactic acid. The safety of hydroxystearic acid was evaluated in 2 separate reviews. In 1999, the Panel published a final report with the conclusion that hydroxystearic acid is safe as a cosmetic ingredient in the present practices of use as described in the safety assessment.[2] Hydroxystearic acid was then included in the report evaluating the safety of fatty acids and fatty acid salts, and in 2019, the Panel concluded that hydroxystearic acid is safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be determined based on a quantitative risk assessment.[3] For lactic acid, the Panel published a final report in 1998 with the conclusion that lactic acid is safe for use in cosmetic products at concentrations ≤ 10%, at final formulation pH ≥ 3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection, and that it is safe for use in salon products at concentrations ≤ 30%, at final formulation pH ≥ 3.0, in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection.[4] The Panel reaffirmed this conclusion, as published in 2017.[5] These reports are available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment pertains to Polylactic Acid use in biomedical applications, and, hence, is not specific to cosmetic use. Data summaries pertaining to these Polylactic Acid uses are provided herein.

CHEMISTRY

Definition and Structure

Polyhydroxystearic Acid (CAS Nos. 27924-99-8; 58128-22-6), Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid (CAS Nos. 26811-96-1; 9051-89-2; 26917-25-9) are polymers synthesized from hydroxy carboxylic acids.[1,CIR Staff] For example, Polylactic Acid is a polymer prepared from lactic acid monomers (Figure 1). The definitions and structures of the ingredients included in this review are provided in Table 1.

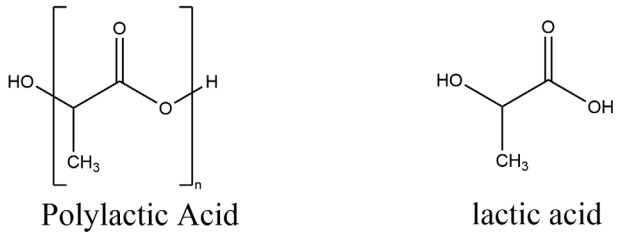


Figure 1. Polylactic Acid and lactic acid

Chemical Properties

The monomer of Polyhydroxystearic Acid, hydroxystearic acid, has a molecular weight (MW) of 300.5 g/mol;[6] however, the mean MW and distribution of weights/lengths is variable and based on reaction conditions. As described by a supplier, Polyhydroxystearic Acid has a number average MW of 1243 g/mol and a weight average MW of 8243 g/mol.[7] Polylactic Acid

has a MW between 53,000 to 800,00 g/mol.[8] The MW of Poly(3-Hydroxyoctanoic Acid) was not found or submitted. Chemical properties for Polyhydroxystearic Acid and Polylactic Acid are further outlined in Table 2.

Polyhydroxystearic Acid is described by a supplier as a 100% active, fully vegetable-derived, polymeric ester with single terminal hydroxy and carboxy groups.[9] At ambient temperatures, Polyhydroxystearic Acid is a yellow, viscous liquid which has numerous nucleophilic sites, and is expected to complex water via hydrogen bonding on the skin. Polyhydroxystearic Acid is soluble in castor oil, mineral oil, isododecane, isopropyl myristate, isononyl isononanoate, and pentaerythrityl tetraethylhexanoate, but is not soluble in water, ethanol, propylene glycol, cyclopentasiloxane, or dimethicone.

Polylactic Acid is a thermoplastic, stiff, glassy material, which has a density of 1.25 g/ml, and a glass transition temperature of 55 °C.[8] Additionally, Polylactic Acid is an aliphatic polyester, which is extremely hydrophobic and is soluble in organic solvents, such as benzene and chloroform, and is not soluble in water, methanol, or ethanol.[10,11] Made from L-, D-, or DL-stereoisomers of lactic acid, Polylactic Acid exists in different enantiomeric forms.[10] This variance in enantiomeric composition affects the crystallization, degradation rate, MW, and glass-transition temperature of the resulting polymer, among other chemical properties; Poly-L-lactic Acid is semi-crystalline, Poly-D-lactic Acid is crystalline, and Poly-D,L-lactic Acid is amorphous.[10,12] In a study describing film-forming Polylactic Acid, exposure to ethanol and water resulted in concurrent hydrolytic degradation, producing changes in MW and release of lactic acid monomer, and crystallization, characterized by swelling of the polymer matrix.[13]

Method of Manufacture

The methods described below are general to the processing of commercial forms of these ingredients. It is unknown if these apply to cosmetic ingredient manufacturing.

Poly(3-Hydroxyoctanoic Acid)

Large-scale synthesis of Poly(3-Hydroxyoctanoic Acid) using the bacterial strain *Pseudomonas putida* GPo1 in lyophilized cell material was evaluated.[14] Three batches of *P. putida* were cultivated, in mineral salts medium containing 20 mM sodium octanoate, as well as sodium hydroxide, ammonium hydroxide, or octanoic acid, at the 400-l scale, in a 650-l capacity bioreactor, for 48 h. Cells were harvested, lyophilized, and extracted with acetone, resulting in 94% recovery of the Poly(3-Hydroxyoctanoic Acid) content in the cells. Subsequent use of a precipitation solvent of methanol and ethanol at a 1:1 ratio resulted in a highly purified Poly(3-Hydroxyoctanoic Acid), which once dried, yielded ~ 99 ± 0.2% (wt/wt) of the polymer.

Polylactic Acid

The main feedstock for Polylactic Acid includes renewable biomass, such as sugarcane, corn, wheat, rice.[11,15] Industrial production of lactic acid, the precursor of Polylactic Acid, is mostly achieved via microbial carbohydrate fermentation, which enables the mass production of optically pure lactic acid, an essential factor in determining the chemical properties of Polylactic Acid.[16]

Direct condensation, azeotropic dehydration condensation polymerization, and ring-opening polymerization methods are used to produce higher MW Polylactic Acid, of which the last is the most efficient.[17,18] Ring-opening polymerization involves the polycondensation of lactic acid monomers to low-MW Polylactic Acid, depolymerization of the Polylactic Acid into lactide, and catalyst-driven ring-opening polymerization of the lactide intermediate.

Impurities

Polyhydroxystearic Acid

According to a supplier, 20% of the MW of Polyhydroxystearic Acid is less than 1000 g/mol, which is attributable to oligomers.[7]

Poly(3-Hydroxyoctanoic Acid)

The purity of Poly(3-Hydroxyoctanoic Acid) precipitated from a salt, using various solvents, was evaluated.[14] Compared to purity resulting from the standard method of dissolving in chloroform and precipitating with ethanol (84 ± 1.5 % (wt/wt)), the highest purity of Poly(3-Hydroxyoctanoic Acid) was achieved from precipitation with ethanol-methanol (70%, v/v) mix, at 99 ± 0.2 %.

Polylactic Acid

Since Polylactic Acid is often produced via the polymerization of commercial lactic acid and lactide, impurities found in these stock solutions can often affect the purity and chemical properties of the resulting Polylactic Acid.[16] Commercial lactic acid solutions are typically 80 - 90% aqueous, containing L-, D-, or D,L-lactic acid, and are also reported to contain the following impurities: arsenic (< 1 ppm), iron (< 5 ppm), heavy metals (< 5 ppm), chloride (< 10 ppm), sulfates (< 10 ppm), sulfated ash (residue after pyrolysis), reducing sugars, methanol, and methyl ester. Commercial lactic acid used for the polymerization of Polylactic Acid often contains water, lactic acid dimers, trimers, and oligomers, and residual catalyst.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2022 VCRP survey data, Polyhydroxystearic Acid is reported to be used in 265 formulations, of which 116 uses are in lipsticks, and Polylactic Acid is reported to be used in 18 formulations (Table 3).[19] Results from a 2021 concentration of use survey, conducted by the Council, indicate Polyhydroxystearic Acid has the highest reported concentration of use; it is used at up to 14.2% in lipsticks.[20] Polylactic Acid is reported to be used at up to 5% in skin cleansing products. Poly(3-Hydroxyoctanoic Acid) is not reported to be in use according to the VCRP and industry survey (Table 4).

Polyhydroxystearic Acid and Polylactic Acid are reported to be used in products that may lead to incidental ingestion and exposure to mucous membranes; for example, as stated above, Polyhydroxystearic Acid is reported to be used in lipsticks at a maximum concentration of 14.2%. These ingredients have also been reported to be used in products that may come in contact with the eyes; for example, Polyhydroxystearic Acid is reported to be used at up to 8% in mascaras. Additionally, Polyhydroxystearic Acid is reported to be used at up to 0.9% in other baby products.

Furthermore, Polyhydroxystearic Acid is reported to be used in aerosol hair sprays at up to 0.5%, as well as in 5 face powder formulations (concentration of use not reported), and could possibly be inhaled. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients, and without consumer habits and practices data or particle size data related to this use technology, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

All 3 ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[21]

Non-Cosmetic

Polyhydroxystearic Acid is a polymer, exempt from the requirement of tolerance due to meeting criteria of a low-risk polymer, as an inert ingredient in pesticide chemical formulations, assuming good agricultural or manufacturing practices [40 CFR 180 § 960]. In 2010, the European Food Safety Authority (EFSA) issued the scientific opinion that Polyhydroxystearic Acid is safe for use in consumer food packaging, provided its migration does not exceed 5 mg/kg food.[22]

The EFSA also issued the scientific opinion in 2010 stating that Polylactic Acid is safe for indirect food contact.[23] Polylactic Acid has versatile use in various industries, such as food packaging, single use products, textiles, automobiles, agriculture, electronics, and construction,[15] and has been approved since 1970 by the FDA to be in contact with biological fluids.[10] Polylactic Acid is also approved by the FDA for use in surgical devices such as sutures, ligatures, and meshes, and is identified as an approved bone grafting material [21 CFR 872 § 3930]. Additionally, the FDA utilizes the Recognized Consensus Standard, ASTM F2579-18, issued by the ASTM International (formerly known as American Society for Testing and Materials) in 2019, which set specifications for amorphous Polylactic Acid used in surgical implants.

Due to its biocompatible and resorbable characteristics, Polylactic Acid also has widespread use in biomedical applications such as drug delivery,[24] tissue engineering,[25] and tumor targeting.[26,27] It is common for Polylactic Acid to be combined with other polymers to form composite substances, notably, in uses such as surgical sutures,[28] bone regeneration,[29] and orthopedic fixtures and devices.[30] Polylactic Acid is also listed as an ingredient in FDA-approved medical devices (surgical tape dressings), as well as in two orthotic devices, a plate and a mesh, used in spinal intervertebral fusion.[31,32]

TOXICOKINETIC STUDIES

Animal

Subcutaneous

Polylactic Acid

In a 90-d study examining the in vivo degradation of Polylactic Acid in rats, an implant chamber containing 100 mg of Polylactic Acid was implanted on either side of the midline, subcutaneously, in 22 rats.[33] Radioactive, [^{14}C]Polylactic Acid was implanted in 15 rats, while the remaining 7 rats were implanted with non-radiolabeled Polylactic Acid to serve as controls. Seven rats (5 with the radiolabeled test article, and 2 controls) were placed in metabolic cages, and urine and feces were collected every 4 d for analysis of radioactivity. After 90 d, these 7 animals were killed and radioactivity was measured in the liver, kidney, lung, heart, brain, spleen, muscles, pouch around the chamber, and the contents of the implant chamber. The remaining 15 rats (10 with the radiolabeled test article and 5 controls) were placed in conventional cages and killed at 2 h, 7 d, 14 d, 1 mo, or 2 mo after implantation. Vital organs and implant chamber contents were analyzed for presence of the radioactive label. A 12-14% loss of the radioactive-labeled polymer was measured in the implants at the end of 3 mo. No significant radioactivity was recovered in the feces or urine of the animals during the 3-mo period, and no radioactivity was found in the vital organs of any of the animals. The authors surmised that these results evidenced the slow biodegradability of Polylactic Acid, as well as the possibility of degradation and elimination via respiration.

TOXICOLOGICAL STUDIES

Toxicological studies were not found in the published literature, and unpublished data were not submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity studies were not found in the published literature, and unpublished data were not submitted.

GENOTOXICITY STUDIES

Details for the genotoxicity studies summarized below can be found in Table 5.

Polylactic Acid film substrates (0.25 cm^2) were not genotoxic to Chinese hamster ovary cell lines in a Comet assay or in an in vitro cytokinesis-blocked micronucleus assay.[34] Groups of 10 mice received an i.p. injection of either saline (negative controls), cyclophosphamide (positive controls), or 0, 50, 100, or 200 ml/kg Polylactic Acid in an in vivo micronucleus test.[35] The incidence of micronucleated polychromatic erythrocytes in mice treated with the low, medium, and high doses of Polylactic Acid extracts was similar to the incidence in the saline-treated group; the test article was considered non-genotoxic. Groups of 5 male rats had a 2-mm thick, 4-mm diameter disc of 95% Polylactic Acid inserted in the calvarium for either 90 or 120 d in a micronucleus test (no test material inserted for controls).[36] The authors deemed the test material as non-genotoxic.

CARCINOGENICITY STUDIES

Carcinogenicity studies were not found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details for the dermal irritation and sensitization studies summarized below can be found in Table 6.

Groups of 2 New Zealand white rabbits had either saline, dinitrofluorobenzene (DFNB), or 0.2 g/ml of Polylactic Acid film extracts (extracted with saline) applied to shaved back skin, via saturated gauze, for 24 h in a skin irritation test.[35] Both of the rabbits treated with the Polylactic Acid film extracts had a primary irritation score of 0 and primary irritation index (PII) of 0; the authors deemed the test article as non-irritating. Polyhydroxystearic Acid was not irritating or sensitizing when tested neat in an occlusive human repeated insult patch test (HRIPT) of 51 subjects.[37] A product containing 3.45% Polyhydroxystearic Acid was not irritating or sensitizing, when tested neat in a modified Marzulli-Maibach HRIPT using 107 subjects; the mean irritation index (MII) calculated for all subjects during induction was 0.[38] Similarly, in a Marzulli-Maibach HRIPT of a product containing 4% Polylactic Acid, using 104 subjects, the authors deemed the test article as a non-irritant and non-sensitizer.[39]

OCULAR IRRITATION STUDIES

According to a supplier, Polyhydroxystearic Acid was determined to have no ocular irritation potential in an in vitro hen's egg-chorioallantoic membrane test (HET-CAM).[9] Additional details were not provided. Further data on the ocular irritation potential of the ingredients reviewed in this safety assessment were not found in the published literature or submitted.

CLINICAL STUDIES

Case Reports

Polylactic Acid

A 30-yr-old woman, a 54-yr-old man, and a 62-yr-old woman, all healthy and with no prior history of cosmetic augmentation, each received repeated treatments with injectable Polylactic Acid (reconstituted with water) to address facial drooping and nasolabial wrinkles due to facial lipoatrophy.[40] No adverse effects were reported in any of the 3 subjects at the 15-mo post-treatment follow-up.

SUMMARY

This report addresses the safety of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid, as used in cosmetic formulations. All 3 of these ingredients are polymers synthesized from hydroxycarboxylic acid monomers. According to the *Dictionary*, these ingredients are reported to function as a non-surfactant dispersing agent, a skin-conditioning agent, and an abrasive, respectively. According to 2022 VCRP data, Polyhydroxystearic Acid and Polylactic Acid are reported to be used in 265 cosmetic formulations and in 18 cosmetic formulations, respectively. The highest concentration of use reported in 2021 for Polyhydroxystearic Acid was 14.2% in lipsticks, and for Polylactic Acid, 5% in skin cleansing products.

Polylactic Acid is approved by the FDA for use in surgical devices such as sutures, ligatures, and meshes and as a food contact substance. The FDA utilizes the Recognized Consensus Standard (ASTM F2579-18), issued by ASTM International in 2019, which set specifications for amorphous Polylactic Acid used in surgical implants.

In a 90-d study, the in vivo degradation of 100 g of [^{14}C]Polylactic Acid implanted in rats was examined. No significant radioactivity was recovered in the feces or urine of the animals during the study period and no significant radioactivity was found in the liver, kidney, lung, heart, brain, spleen, muscles, and pouch around the implant chamber upon necropsy. At the end of 3 mo, a 12-14% loss of radioactive-labeled polymer was measured in the contents of implant chamber. The authors surmised that these results evidenced the slow biodegradability of Polylactic Acid, as well as the possibility of its degradation and elimination via respiration.

Polylactic Acid film substrates (0.25 cm^2) were not mutagenic to Chinese hamster ovary cell lines in a comet assay or in an in vitro cytokinesis-blocked micronucleus assay, when compared to 0.25 µM doxorubicin or untreated controls. In an in vivo micronucleus test, the incidence of micronucleated polychromatic erythrocytes in mice injected twice, with 50, 100, or 200 ml/kg Polylactic Acid film extracts/injection, were comparable to saline-injected controls; the test article was not considered genotoxic. The genotoxic potential of 95 % Polylactic Acid discs was evaluated in groups of 5 male rats in a micronucleus test following insertion of the discs in the calvarium for up to 120 d. No significant decreases in the frequency of polychromatic erythrocytes or increases in micronucleated polychromatic erythrocytes were observed in test animals, compared to untreated controls; the test article was considered non-genotoxic.

In a 24-h occlusive patch test, 0.2 g/ml of a Polylactic Acid film extract (extracted with saline) was not irritating to New Zealand white rabbit skin; both of the rabbits treated with the Polylactic Acid extracts had a primary irritation score of 0 and PII of 0. Polyhydroxystearic Acid was not irritating or sensitizing when tested neat in an occlusive HRIPT of 51 subjects. A product containing 3.45% Polyhydroxystearic Acid was not irritating or sensitizing when tested neat in a modified Marzulli Maibach HRIPT of 107 subjects. The MII calculated for all subjects during induction was 0. Similarly, a product containing 4% Polylactic Acid was deemed a non-irritant and a non-sensitizer when tested neat in a Marzulli-Maibach HRIPT using 104 subjects.

The ocular irritation potential of Polyhydroxystearic Acid was evaluated in vitro. Polyhydroxystearic Acid was determined to have no ocular irritation potential in the HET-CAM test.

A healthy 30-yr-old woman, 54-yr-old man, and a 62-yr-old woman each received repeated treatments of injectable Polylactic Acid to address facial lipoatrophy. No adverse effects were observed over a 15-mo post-treatment period.

DISCUSSION

The Panel assessed the safety of Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid) and Polylactic Acid as used in cosmetic formulations. The Panel reviewed the available data and concluded that these 3 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

The Panel discussed that these ingredients are large molecules that are not likely to be absorbed. The Panel stated that while the monomers used to make these ingredients are of different sizes and can polymerize into different physical forms (i.e., liquids or solids), the structural connectivity and features of the resulting polymers would be very similar. Additionally, the Panel noted these monomers would be the primary impurities and decomposition products of oligomers (including dimers and trimers) present in these polymers. The Panel considered its prior safety determinations of the corresponding monomers of these ingredients, in which they had reviewed safety at concentrations that were much higher than those reported for the

polymers reviewed in this assessment. Thus, it was determined that the safety profile of these polymeric ingredients would not differ from that of the monomers.

The Panel noted the lack of systemic toxicity data, including a lack of developmental and reproductive toxicity and carcinogenicity data. However, concerns regarding systemic toxicity of these ingredients were mitigated by the approved use in food contact materials, multiple FDA-approved uses of Polylactic Acid in medical devices, the existing 2019 ASTM International standard for the use of amorphous Polylactic Acid in surgical implants, the very low likelihood of absorption, and the safety of the monomers used to manufacture these ingredients.

Negative dermal irritation and sensitization data included in this review reassured the Panel of the dermal safety of these ingredients. The Panel particularly noted that undiluted Polyhydroxystearic Acid was not irritating or sensitizing when tested in an occlusive HRIPT of 51 subjects, and that two separate products containing 3.45% Polyhydroxystearic Acid and 4% Polylactic Acid were neither irritating nor sensitizing when tested neat in HRIPTs using 107 and 104 subjects, respectively.

Furthermore, the Panel discussed the issue of incidental inhalation exposure resulting from these ingredients; for example, Polyhydroxystearic Acid is reported to be used at 0.5% in aerosol hair sprays. Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Therefore, the Panel has concluded the data are insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 3 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

Polyhydroxystearic Acid
Polylactic Acid
Poly(3-Hydroxyoctanoic Acid)*

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

TABLES

Table 1. Definitions, structures, and reported functions of the ingredients in this assessment[1, CIR Staff]

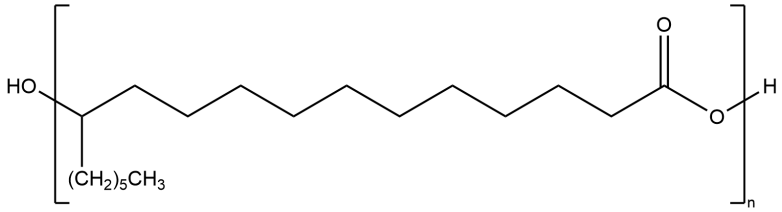
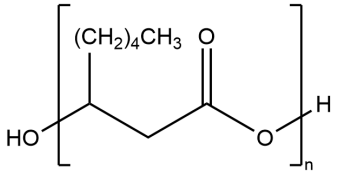
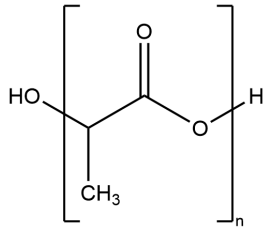
Ingredient	Definition	Function
Polyhydroxystearic Acid 27924-99-8 58128-22-6	Polyhydroxystearic Acid, defined as a polymer of hydroxystearic acid, generally conforms to the structure: 	Dispersing agents - nonsurfactant
Poly(3-Hydroxyoctanoic Acid)	Poly(3-Hydroxyoctanoic Acid) is the polymer of 3-hydroxyoctanoic acid produced through fermentation that conforms generally to the structure: 	Skin-conditioning agents - miscellaneous
Polylactic Acid 9051-89-2 26917-25-9 26811-96-1	Polylactic Acid, defined as a polymer of lactic acid, generally conforms to the structure: 	Abrasives

Table 2. Chemical properties of Polyhydroxystearic Acid and Polylactic Acid

Property	Value	Reference
Polyhydroxystearic Acid		
Physical Form	Viscous liquid or waxy solid	9
Color (Gardner color standard)	3; yellow	9
Odor	Mild, bland	9
Molecular Weight (g/mol)	1243 (number average) 8243 (weight average)	7
Refractive Index (@ 25 °C)	1.4675	9
Specific Gravity (@ 25 ºC)	0.9333	9
Solubility		9
Soluble	castor oil, mineral oil, isododecane, isopropyl myristate, isononyl isononanoate, pentaerythrityl tetraethylhexanoate	
Insoluble	water, ethanol, propylene glycol, cyclopentasiloxane, dimethicone	
Polylactic Acid		
Physical Form	Stiff, glassy material	8
Color	Colorless	8
Glass Transition Temperature (°C)	55	8
Molecular Weight (g/mol)	53,000 – 800,000	8
Density (g/cm^3)	1.25	8
Solubility		8,10,11
Soluble	benzene, chloroform, furan, 1,4-dioxane, 1,3-dioxolane, pyridine, and tetrahydrofuran	
Insoluble	acetonitrile, alcohols, ethanol, methanol, and water	

Table 3. Frequency (2022)[19] and concentration (2021)[20] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Polyhydroxystearic Acid		Polylactic Acid	
Totals	**265**	**0.014 – 14.2**	**18**	**0.084 - 5**
summarized by likely duration and exposure*				
Duration of Use				
Leave-On	*259*	*0.014 – 14.2*	*13*	*0.084*
Rinse-Off	*6*	*NR*	*5*	*3.5 - 5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type*				
Eye Area	62	0.12 - 8	3	NR
Incidental Ingestion	116	0.4 – 14.2	1	0.084
Incidental Inhalation-Spray	10[a]; 9[b]	0.5; 0.2 -8[a]	5[a]; 1[b]	NR
Incidental Inhalation-Powder	5; 9[b]	0.014 -0.88[c]	1[b]	NR
Dermal Contact	138	0.014 - 10	16	3.5 - 5
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	4	0.5 - 8	1	NR
Hair-Coloring	5	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	116	0.4 – 14.2	2	0.084
Baby Products	2	0.9	NR	NR
as reported by product category				
Baby Products				
Other Baby Products	2	0.9		
Eye Makeup Preparations				
Eyebrow Pencil	10	0.4-0.72		
Eyeliner	26	0.4		
Eye Shadow	14	NR	3	NR
Eye Lotion	1	0.12		
Mascara	2	8		
Other Eye Makeup Preparations	9	0.18		
Hair Preparations (non-coloring)				
Hair Conditioner			1	NR
Hair Spray (aerosol fixatives)	NR	0.5		
Tonics, Dressings, and Other Hair Grooming Aids	2	8		
Other Hair Preparations	2	NR		
Hair Coloring Preparations				
Hair Tints	5	NR		
Makeup Preparations				
Blushers (all types)	4	0.11-0.3		
Face Powders	5	NR		
Foundations	6	0.1-0.22		
Leg and Body Paints	1	NR		
Lipstick	116	0.4-14.2	1	0.084
Makeup Bases	6	NR		
Makeup Fixatives	1	NR		
Other Makeup Preparations	25	0.25		
Personal Cleanliness Products				
Bath Soaps and Detergents			1	NR
Skin Care Preparations				
Cleansing	1	NR	3	5
Face and Neck (exc shave)	9	0.014-0.88 (not spray)	1	NR
Body and Hand (exc shave)	NR	0.1 (not spray)		
Moisturizing	8	0.15-10 (not spray)	5	NR
Paste Masks (mud packs)			NR	3.5
Other Skin Care Preparations	10	0.49-1.5	3	NR
Suntan Preparations				
Other Suntan Preparations	NR	0.2-0.3		

NR – not reported

*likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

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

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

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

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

Table 4. Ingredient not reported to be in use[19,20]

Poly(3-Hydroxyoctanoic Acid)

Table 5. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Polylactic Acid film substrates	0.25 cm^2	NR	Chinese hamster ovary cell lines	Comet assay. Cells were exposed for 24 h to either the Polylactic Acid film, 0.25 µM doxorubicin (positive control), or no treatment (negative controls).	Not genotoxic	[34]
Polylactic Acid film substrates	0.25 cm^2	NR	Chinese hamster ovary cell lines	In vitro cytokinesis-blocked micronucleus assay. Same protocol as described above, with the addition of 5 µg/ml cytochalasin-B for an additional 24 h prior to fixing and preparation of slides.	Not genotoxic	[34]
IN VIVO						
Polylactic Acid film extracts	0, 50, 100, or 200 ml/kg	fetal bovine serum, containing RPMI-1640 and diluted in saline	Groups of 10 mice	Micronucleus test. Animals received an intraperitoneal injection of either saline (control), the test article, or cyclophosphamide (positive control; 40 mg/kg) and a received a 2nd injection of the same treatment 24 h later.	Not genotoxic; The incidences of micronucleated polychromatic erythrocytes in mice treated with the low, medium, and high doses of Polylactic Acid extracts were 2.0, 2.2, and 2.3%, respectively, which was similar to the incidence in the saline-treated group. Positive controls produced expected results.	[35]
95% Polylactic Acid	2 mm-thick, 4-mm diameter disc		Groups of 5 male rats	Micronucleus test. The discs were inserted in the calvarium of 2 groups, one observed for 90 d and the other observed for 120 d, before being killed. No test material was inserted for controls. Both control and treatment groups received the same surgical procedures and pre- and post-operative medications (0.5 mg/100 g ketamine and 0.025 ml/100g xylazine). Bone marrow was extracted and stained on slides to identify the presence of micronucleated polychromatic erythrocytes.	Not genotoxic; Upon staining of bone marrow extracts, no significant decreases in the frequency of polychromatic erythrocytes or increases in micronucleated polychromatic erythrocytes were observed in the test animals, compared to controls.	[36]

Abbreviations: NR – none reported; RPMI – Roswell Park Memorial Institute

Table 6. Dermal irritation and sensitization studies

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
ANIMAL					
Polylactic Acid film extracts	0.2 g/ml, extracted with saline	New Zealand white rabbits (2/group)	24-h skin irritation test. Fur was removed from the animal backs 24 h prior to the test, and sterile gauze was used to cover the skin area. Either saline, DNFB, or the Polylactic Acid extract were applied to the sterile gauze until it was fully soaked. The gauze was removed after 24 h and the skin condition was observed 1, 24, 48, and 72 h after patch removal. A primary irritation index value was calculated using the primary skin irritation score for each animal divided by the total number of animals.	Not irritating; both rabbits treated with Polylactic Acid extracts had a primary irritation score of 0 and PII = 0.	[35]
HUMAN					
Polyhydroxystearic Acid	0.2 g; tested neat	51 subjects	HRIPT; 9 occlusive, 24-h induction applications were made over a 3-wk period. Induction sites were scored 24 h after patch removal. After a 10-14 d non-treatment period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications. The reactions were scored at 24 and 48 h after application.	Not irritating or sensitizing; no adverse reactions occurred.	[37]
Polyhydroxystearic Acid; 3.45% in a product	0.02 g, , tested neat	107 subjects	Modified Marzulli Maibach HRIPT; 9 occlusive applications were made to a 50 mm^2 area of the back over a 3-wk period. The 1st, 2nd, 4th, 5th, 7th, and 8th applications were made for 48 h, and the 3rd, 6th, and 9th applications were made for 72 h. After a 13-d non-treatment period, a single 48-h challenge application was made to the induction site and a previous untreated site. Reactions were scored on a 0-4 irritation scale between 15 and 35 min of patch removal during both the induction and challenge phases; challenge phase reactions were additionally evaluated 24 h and 48 h after application. An MII was calculated by dividing the sum of the quotations of the 9 induction readings by the number of subjects and readings performed.	Not irritating or sensitizing, MII = 0	[38]
Polylactic Acid; 4% in a product	0.02 ml, tested neat	104 subjects	Marzulli Maibach HRIPT; 9 occlusive, 48-h induction applications were made using 8 mm Finn chambers to the same site over a 3-wk period. Induction sites were evaluated for dermal reactions immediately prior to application of the next patch. After a 10-14 d non-treatment period, challenge applications were made for 48 h to the original test site and a previously untreated site in the same manner as the induction applications. Challenge sites were scored 48, 72, and 96 h after application.	Not irritating or sensitizing	[39]

Abbreviations: DNFB- dinitrofluorobenzene; HRIPT – human repeated insult patch test; MII – mean irritation index; PII – primary irritation index

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