Safety Assessment of Levulinic Acid and Sodium Levulinate as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	February 16, 2021
Panel Meeting Date:	March 11-12, 2021

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.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR.

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

Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Preethi S. Raj, M.Sc.
Senior Scientific Analyst/Writer, CIR

Date: February 16, 2021

Subject: Safety Assessment of Levulinic Acid and Sodium Levulinate as Used in Cosmetics

Enclosed is the Draft Tentative Report of the Safety Assessment of Levulinic Acid and Sodium Levulinate as Used in Cosmetics (identified as *levaci032021rep* in the pdf). This is the second time the Panel is seeing a safety assessment of these cosmetic ingredients. At the September 2020 Panel Meeting, the Panel issued an Insufficient Data Announcement (IDA), and the following data were requested. No data have been received.

- Impurities
- 28-day dermal toxicity data; if absorbed, other endpoints, e.g. developmental and reproductive toxicity data, may be needed
- Ocular irritation data at, or above, the highest reported leave-on concentration, 0.57%

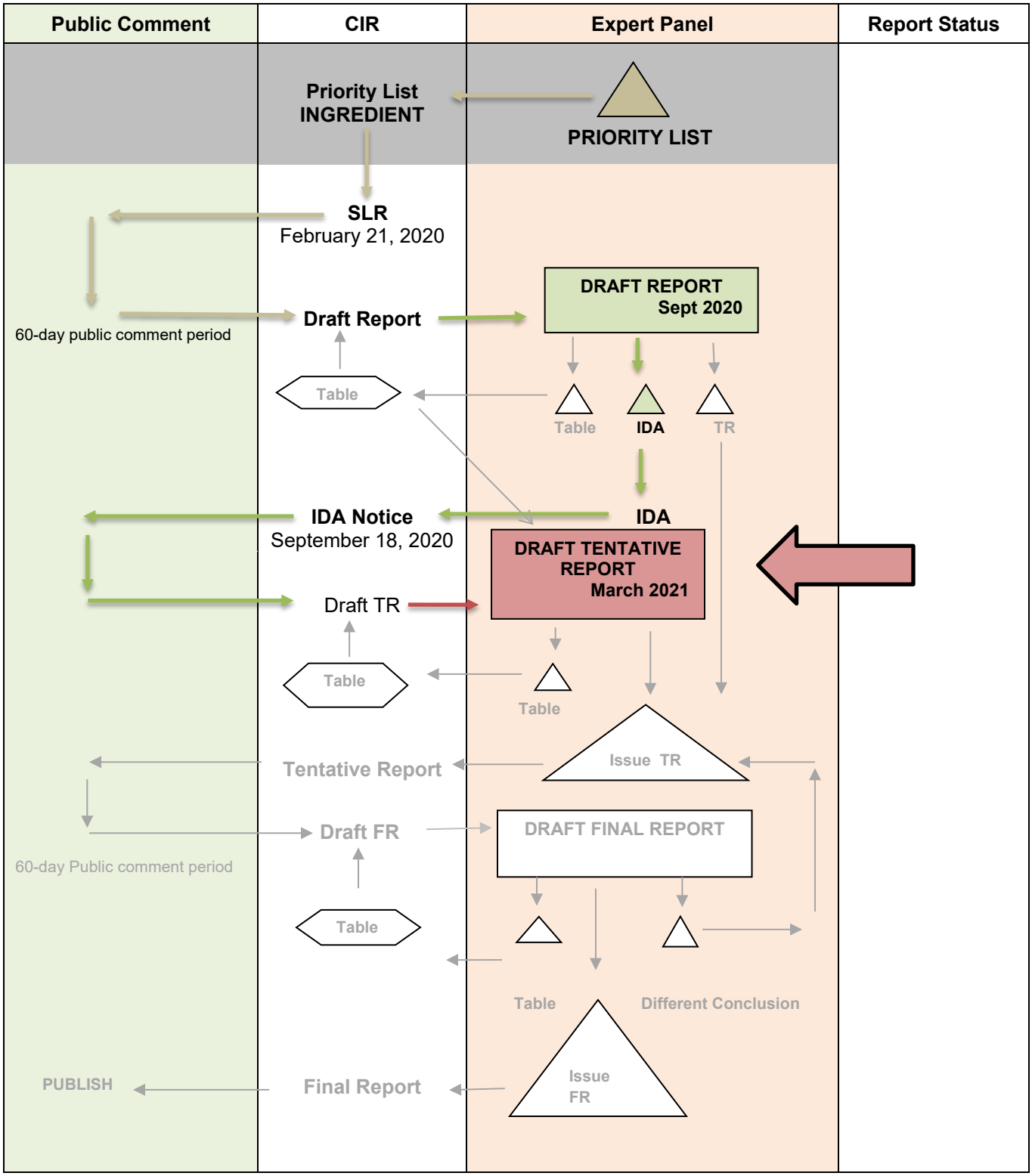
Also included in this package, for your review, are a flow chart (*levaci032021flow*), literature search strategy (*levaci032021strat*), ingredient data profile (*levaci032021prof*), transcripts from the previous meeting (*levaci032021min*) and an ingredient history (*levaci032021hist*). Data from 2021 FDA VCRP have been received and incorporated (*levaci032021FDA*). Use categories have remained the same, with an overall decrease in reported uses, from the previous year. Total reported uses of Levulinic Acid decreased from 131 to 98 formulations, while total reported uses of Sodium Levulinate decreased from 402 to 295 formulations. Changes in the text reflecting updated VCRP data are highlighted in yellow.

Based on the proceedings and comments from the September 2020 meeting, a draft Discussion has been prepared; however, additional discussion points are requested. After reviewing these documents, the Panel should issue a Tentative Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Levulinic Acid & Sodium Levulinate

MEETING March 2021



CIR History of:

Levulinic Acid and Sodium Levulinate

January 2019

-Concentration of use data submitted by Council

January 2020

-FDA frequency of use data obtained

February 2020

-Levulinic Acid and Sodium Levulinate SLR posted on the CIR website

Data received: March 2, 2020: Two HRIPTs for 0.4011% and 0.57% Sodium Levulinate

September 2020

- A Draft Report was presented to the Panel. An IDA was issued, during which the following were requested:

- Impurities
- 28-day dermal toxicity data (and, if found to be absorbed other endpoints may be needed, e.g. developmental and reproductive toxicity (DART))
- Ocular irritation data at, or above, the highest reported leave-on concentration, 0.57%

No additional data have been received.

January 2021

New VCRP data were received

March 2021

-A Draft Tentative Report is being presented to the Panel.

Levulinic Acid and Sodium Levulinate Data Profile* – March 11-12th, 2021 – 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
Levulinic Acid	X	X	X	X	X		X	X			X				X				X	X	X		X	X		X			
Sodium Levulinate	X	X		X		X																X		X					

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

Levulinic Acid and Sodium Levulinate

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Levulinic Acid; 4-oxovaleric acid	123-76-2	✓	✓*	✓*	✓	✓*	✓	NR	NR	NR	✓*	✓*	✓	NR	✓	NR	NR	✓	✓
Sodium Levulinate; Sodium 4-oxovalerate	19856-23-6	✓	✓*	✓*	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	

NR – not reported or available
✓ - data is available
✓*- in database, but data is not available or relevant
total # useful/total # of hits

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet - total # useful/ total number of hits*]

Sodium Levulinate – 2/6
Levulinic Acid – 3/926
"123-76-2" AND toxicity – 1/7
"19856-23-6" - 4/346
(((levulinic acid) OR "123-76-2") AND oral toxicity) - 0/1
(((levulinic acid) OR "123-76-2") AND chemical structure) – 3/432
(((levulinic acid) OR "123-76-2") AND manufacturing) – 0/4
(((levulinic acid) OR "123-76-2") AND impurities) – 1/6
((((levulinic acid) OR "123-76-2") AND toxicokinetics)) - 3/25
((((levulinic acid) OR "123-76-2") AND dermal penetration)) - 0/0
((((levulinic acid) OR "123-76-2") AND inhalation)) -0/2
((((levulinic acid) OR "123-76-2") AND acute toxicity)) – 0/2
((((levulinic acid) OR "123-76-2") AND short term toxicity)) - 0/0
((((levulinic acid) OR "123-76-2") AND subchronic toxicity)) – 0/0
((((levulinic acid) OR "123-76-2") AND chronic toxicity)) – 0/2
((((levulinic acid) OR "123-76-2") AND developmental toxicity)) – 0/2
((((levulinic acid) OR "123-76-2") AND reproductive toxicity)) – 0/1
((((levulinic acid) OR "123-76-2") AND cancer)) -0/87
((((levulinic acid) OR "123-76-2") AND mutagenicity)) – 1/1
((((levulinic acid) OR "123-76-2") AND genotoxicity)) – 0/0
((((levulinic acid) OR "123-76-2") AND cytotoxicity)) – 0/8
((((levulinic acid) OR "123-76-2") AND dermal irritation)) – 0/0
((((levulinic acid) OR "123-76-2") AND dermal sensitization)) – 0/0
((((levulinic acid) OR "123-76-2") AND phototoxicity)) – 1/2
((((levulinic acid) OR "123-76-2") AND ocular irritation)) – 0/0
((((levulinic acid) OR "123-76-2") AND mucous membrane irritation)) – 0/0
((((levulinic acid) OR "123-76-2") AND case reports)) -0/22
((((levulinic acid) OR "123-76-2") AND adverse events)) – 1/1
((((levulinic acid) OR "123-76-2") AND epidemiology)) – 0/4

General Search

Levulinic acid cosmetic use
Sodium Levulinate cosmetic use

Typical Search Terms

- INCI names
- CAS numbers

- **chemical/technical names:**
  - **Levulinic Acid:**
    - 3-Acetylpropionic Acid – 0/2,952,706
    - 4-Ketovaleric Acid-0/2
    - 4-Oxopentanoic Acid [AND toxicity] – 0/6
    - 4-Oxovaleric Acid -1/2
    - Pentanoic Acid, 4-Oxo-2/30
  - **Sodium Levulinate:**
    - Pentanoic Acid, 4-oxo-, Sodium Salt – 0/0
- additional terms will be used as appropriate

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

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;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- 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
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
- 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/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- 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
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.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

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – http://www.ifraorg.org/
- Research Institute for Fragrance Materials (RIFM)

SEPTEMBER 2020 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – September 14, 2020

DR. BELSITO: And this is also the first time we're looking at this: Levulinic Acid and Sodium Levulinate. And, again, we got comments from Council on this which I presume will be incorporated.

I just had a question to Dan because, when I first saw this, I was going to look for phototoxicity data because amino Levulinic Acid we use to absorb blue light in treating precancers of the skin, but I'm assuming it's the addition of the amine group that makes it absorbed in visible range?

DR. LIEBLER: I can't imagine why amino Levulinic Acid would absorb light, but I can tell you that this won't, at least in the UV vis, you know. It's relevant to bio activity. No, this doesn't.

DR. BELSITO: Okay. And, the impurities, do we need based upon the manufacturing methods?

DR. LIEBLER: No, this was acceptable to me.

DR. SNYDER: No, sorry. I had a question for Dan. The acceptance criteria for food grade is 97 percent purity, but we don't -- is that similar to the cosmetics grade then? Do we know?

DR. LIEBLER: Yeah, I took that as being also indicative of what's likely to be cosmetic-ingredient grade, but you know, it's -- I couldn't swear that this is the same: food and cosmetic.

DR. SNYDER: It just struck me that this is the first I've ever seen the criteria for food-grade purities, so I wonder if there's a reason why or something.

DR. LIEBLER: There are a lot of --

DR. BELSITO: I think we've dealt this before, Paul, where we had purities for food grade, and we assumed that it would be of a similar purity, no?

DR. SNYDER: Okay. Thank you.

DR. LIEBLER: I would assume the cosmetic market is a small subset of the food-grade market anyway.

DR. BELSITO: Okay. So it's highest leave on is in eye shadows at 0.57. And it is a penetration enhancer, which I guess would need to be in the discussion. We don't have any absorption data, so I think we need a 28-day data to clear DART, no? Paul, Dan, Curt?

DR. SNYDER: Yes.

DR. LIEBLER: Yep.

DR. BELSITO: Um.

DR. SNYDER: I guess we do have a dermal acute study, but that's not good enough, yeah.

DR. BELSITO: Yeah. And the other question is do we need ocular irritation and concentration of use given the highest uses are on the eyes, or are we happy with the ocular irritation?

DR. SNYDER: No, I think it is. Yeah. We have data, so I think we're going to have to say it's --

DR. BELSITO: I mean, because all the information we have suggested it could be quite irritating.

DR. SNYDER: Yes. Yep.

DR. BELSITO: So right now, we have insufficiencies for 28-day dermal and, if absorbed, we would need other endpoints. In the discussion, penetration enhancement and respiratory boilerplate. I thought the sensitization was okay. I just had one question on PDF page 14 and that was -- it says that -- let me remove my comment -- "tested substance was" -- this is right at the bottom of the page -- "The test substance was determined to be a potential skin sensitizer with SI values higher than 1.6 in the mid- and high- dose groups."

With an LLNA, you want an SI of three or greater, so I don't know why they're saying that it was determined be a potential skin sensitizer. I don't know how they drew that conclusion. So, I mean, I don't -- this is a summary from ECGA, so I'm not sure that you're not going to get more information. But we have adequate sensitization studies, so just check that to make sure that that's, in fact, what they're saying because usually the SI has to be three or higher to be considered a sensitizer.

MS. RAJ: Thank you.

DR. BELSITO: So, I mean, at this point, we're insufficient for 28-day dermal to clear DART and other endpoints in ocular irritation at concentration of use but no other data. Is that correct?

DR. SNYDER: Yes, at this point.

DR. LIEBLER: Yep.

DR. BELSITO: Okay.

DR. LIEBLER: Don, one clarification on the Levulinic Acid on photosense, the amino Levulinic Acid doesn't absorb UV or visible light, but it's a precursor for heme synthesis. So, if you give this to somebody, it drives additional heme synthesis, and that does absorb light. So that's the photodynamic therapy connection there.

DR. BELSITO: Okay.

DR. LIEBLER: So it's not technically absorbing; it just drives heme synthesis.

DR. BELSITO: Okay. Thanks, Dan. Okay. Anything else on Levulinic Acid?

MS. RAJ: Just to clarify, were you saying that you -- in the data needs, you might be asking for data for ocular irritation at the present concentration of use. Is that what I heard?

DR. BELSITO: Yes.

MS. RAJ: Okay. Thank you.

DR. BELSITO: Two data needs: 28-day dermal and, if absorbed, other tox endpoints, particularly DART and ocular irritation at concentration of use.

MS. RAJ: Thank you.

DR. BELSITO: And anything else? Wow, we're moving through these more quickly than I thought. Okay. So then Ubiquinone.

Marks Team – September 14, 2020

DR. MARKS: Next is Levulinic. Let me see here.

MS. RAJ: Good morning, everyone.

DR. PETERSON: Hi.

DR. MARKS: Hello, there.

MS. RAJ: And welcome to Dr. Cohen. Nice to meet you virtually.

DR. MARKS: Good. Thank you, Preethi. Okay. This is a draft report. It's the first time we've seen these two ingredients. It's found in foods. They are found in foods. There are no significant absorption of ultraviolet light 290 to 700 nanometers. It is a penetration enhancer, so at least that, I think, needs to be in the discussion. Lisa, Ron, Tom, are the ingredients okay -- these two ingredients?

DR. PETERSON: Well, they don't specify -- I mean, they seem fine, but they don't specify what the impurities are, the 3 percent. It's purest up to 97 percent but what that remaining 3 percent is. Again, I don't have any concerns, but I think it's worth finding out what is known about that other 3 percent. Is it water? Is it -- what is it?

DR. MARKS: What page is that, Lisa, you're on?

DR. PETERSON: Give me a minute. I print things out, and I don't always put the pages on.

MS. RAJ: It's PDF page 11 of the binder.

DR. MARKS: That would mean, Lisa, we would have an insufficient data announcement.

DR. PETERSON: Yeah.

DR. MARKS: Tom, Ron?

DR. HELDRETH: I will add that, if you look, the reference this comes from is the U.S. Pharmacopeia. So what this is, is instead of listing what the actual impurity is per se by a supplier -- but this is more of a specification. So the Pharmacopeia may not have that information to what that other 3 percent is. But certainly a supplier may be able to provide what the impurities would be.

DR. MARKS: So that would be one need would be what is that 3 percent of impurities.

DR. PETERSON: Yeah. I would say --

DR. ANSELL: There's not 3 percent of impurities. The specification is it be at least 97 percent pure.

DR. PETERSON: Right, right, right. But I think because the starting material is biological and different sources, I think you want at least some assurance that nothing -- yeah -- that there's nothing there that's harmful. Again, the concerns are not -- it looked to me like overall it was an ocular irritant, but it was overall safe. But just for due diligence, I think it's interesting to see what they've been analyzed for and what you can exclude as possibilities.

DR. BERGFELD: This is Wilma. Do you think that the original ingredients of sugars and starches from which is comes is helpful?

DR. PETERSON: I think it's helpful, but when you see that some things can have heavy metals in it, you know, that come from algae or --

DR. BERGFELD: Well, we have a heavy metal boilerplate that we can put in our discussion.

DR. HELDRETH: We should also be aware --

DR. COHEN: What is that heavy metal boilerplate?

DR. MARKS: What, David?

DR. BERGFELD: The heavy metal boilerplate.

DR. MARKS: Yeah. David, we have -- for things that come up repeatedly, we have what we used to refer to as boilerplates and still do. But now, I think the more recent terminology is resource document. And so things like pesticides, we have a resource document which we plug in and say pesticides shouldn't be above such and such whatever.

We have the same for heavy metals. We have the same for inhalation, and there are a number of toxicologic endpoints that we handle using this resource document. So as Wilma was implying, if an impurity is heavy metals, we put the heavy metal resource document in, and it alerts the formulator that it shouldn't -- or the manufacturer -- it shouldn't have above a certain level of heavy metals. I think I have that perspective correct. Is that right, Wilma and Bart?

DR. HELDRETH: Yes, that's correct. It's something we typically apply to the botanical-type ingredients. The resource document that you referred to is on the CIR website under the findings section. I can show you a portion of this, if that's helpful.

DR. COHEN: I can look at it after, not to hold the process up.

DR. MARKS: Here we go. We refer to it as boilerplates here. Okay.

DR. ANSELL: Right. And I think the boilerplate is useful, but it's not suggesting that these specific materials have excessive amounts of heavy metals. It's more of a warning that, since this material is grown naturally or derived from a natural material, that the presence of heavy metals and pesticides should be considered as opposed to a conclusion that any specific level in this specific material would be acceptable.

DR. PETERSON: And they don't -- the method of manufacturing doesn't have any statement about how they purify the compound, so I would accept -- so I'll defer to the experience of the group. My reaction to this is that we don't have a method of purification, so the question is what are those impurities. And again, it's more of a making sure that all of the I's are dotted an T's crossed. And Ron and Tom, I guess, sort of what are your experience and what was your reaction?

DR. SHANK: My only toxicology concern was the potential for severe eye irritation. The concentration used in that report was not stated. I think it was 100 percent, but it doesn't say so. But that can be handled when you say safe when used and formulated not to be irritating, especially to the eye. That was my only toxicological concern.

DR. SLAGA: I didn't -- I had the same one, but since it was used at 100 percent, I didn't think that was necessary. The 3 percent impurities, it depends what level the ingredient is being used at. If it's extremely low, 3 percent would be extremely low. So it's a function of -- but this is the first time. I agree with Lisa. It would be nice to see what kind of response you get back.

DR. ANSELL: So this is Jay. The first review, it's entirely appropriate. But before we get our mind set on this, it is not 3 percent impurities. It's 97 percent pure, and the question as to what the other 3 percent is is appropriate. But we should not consider them to be impurities. It could be, for example, water or ethanol.

DR. PETERSON: Right, right. Absolutely. If it's water, there's no concern there. Totally, yes.

DR. ANSELL: Let me also add that its primary function was actually as a fragrance flavor, and RIFM just completed their review in April. So there's significant data available from the RIFM review on this material as well.

DR. PETERSON: Was that consulted for this document?

MS. RAJ: Yes, it was. The data from that assessment has been included in this, Lisa.

DR. PETERSON: And what did they say about the purity -- or do they have a similar comment?

MS. RAJ: Let me see. I have that document open.

DR. MARKS: While you're looking that up, Preethi, Ron, you had not problems with DART?

DR. SHANK: Correct.

DR. MARKS: Okay. Good. So I agree that our two -- we'll be seconding tomorrow, so it'll be interesting to see what the Belsito team thinks. I had safe when formulated to be nonirritating. I'll mention certainly, Lisa, about the 97 percent pure in the composition but clarify what the other 3 percent is. Jay, I will not use the word "impurity."

It is irritating. It's actually a potential sensitizer. So in the discussion, that'll need to be addressed. But the human max and the HRIPT were okay at or above the use concentration, so I think we don't need to put any issues as far as sensitization is concerned. But I like, Ron, to formulate to be nonirritating. Did you, Preethi, find --

MS. RAJ: Yes. Looking at the document, I haven't really seen anything on impurities. There's some information on chemical properties, but not so much impurities. Bart, do you see anything else?

DR. HELDRETH: No, I just see a description of the chemical. I mean, the closest thing they get to speaking on impurities is something that they pulled from the Merck Index just saying that it's colorless, leafy crystals when pure; yellowish when it's commercial grade; and it's almost odorless. But if it decomposes, then there's a pungent, acidic odor. So it's pretty easy to tell if there's some impurities there, but that's from the Merck Index. And the primary reference pulls back to 1969, so I'm not sure that we can rely too much on the validity of that. But again, it's more like a -- it reads more like a specification than an actual analysis of the cosmetic agreement.

DR. ANSELL: I would agree. It's an appropriate question.

DR. PETERSON: So I think if it passes Dan's sniff test, then it passes my sniff test -- so in that I'll come into whatever they propose to move on tomorrow.

DR. MARKS: Lisa, I will directly ask Dan that, and I'll use that sniff test. I like that.

DR. HELDRETH: Particularly for a fragrance.

DR. MARKS: Dan's the stickler, as you said earlier, on method of manufacturing and impurities. Even though this is not an impurity, we just don't know what the other 3 percent composition is and ask Dan whether that was an alert for him. So I think our team tomorrow will be flexible. We'll be seconding whatever the Belsito team proposes, unless it's way out in left field or way out in right field or out of the ballpark. But at any rate, most likely it's going to be a tentative report with a safe when formulated to be nonirritating conclusion, but I'll bring up the issue should we do an insufficient data announcement and clarify what the other 3 percent composition is. And Lisa, I may refer to you and then also Dan, too, and get you two in a discussion.

MS. RAJ: One question quickly. Thank you, all. What type of language would you like to see in the discussion for the penetration enhancement?

DR. MARKS: Ron?

DR. SHANK: I didn't hear a thing. I'm sorry.

MS. RAJ: No, I'm sorry. I caught that because there is some data on Levulinic acid being a penetration enhancer that that should be mentioned in the discussion.

DR. SHANK: Yes.

MS. RAJ: So, I just wanted to ask you all what kind of language you'd like to have added to that effect?

DR. SHANK: I don't see it as a problem.

DR. MARKS: I think noting it, and we've done that in previous reports, Preethi, although I can't bring one up to mind directly.

MS. RAJ: Okay.

DR. MARKS: But just noting that it can be.

MS. RAJ: Okay.

DR. MARKS: Obviously, it was not a toxicologic concern that we felt it would be an insufficient data.

MS. RAJ: Okay.

DR. SLAGA: I agree with Ron. I had no concern for it related to any toxicological effect.

DR. BERGFELD: This is Wilma. I think that on occasion we have suggested it not be applied to damaged skin when sensitive or be considered when applied to damage skin.

MS. RAJ: Right.

DR. HELDRETH: Yes. We've also had some language in the past where we'll say something to the effect of caution should be used when formulating with other ingredients because who's safety was based on a lack of penetration. We've had that kind of language multiple times, I think. Maybe that's what's applicable here, but that's up to you all if you think that's worthwhile.

DR. SHANK: It's used -- max leave on is 0.57 percent, I believe, and it's a food additive. So, anything that might increase the absorption is probably going to not have any toxicological effect.

MS. RAJ: Okay. And of course --

DR. SHANK: The only problem I see for adverse health effect is irritation.

MS. RAJ: Yes. And for the irritation, am I hearing, again, based on what the consensus is tomorrow, that you all are saying when formulated to be nonirritating for the eye and the skin? Because sensitization, I think I heard that, but I don't recall in the report being any dermal sensitization.

DR. SHANK: Right. For the eye.

MS. RAJ: The eye. Okay. Thank you.

DR. MARKS: Yeah. Formulate to be nonirritating, I'm not sure that we need to put eye, just nonirritating.

MS. RAJ: Okay.

DR. MARKS: It was a sensitizer at the local lymph node assay, so that was the alert for sensitization. But again, as I mentioned, the human max and the HRIPT was okay at or above the use concentration. So that reinforces the safety of it from a sensitization point of view. Okay.

Any others? So tomorrow, I'll be seconding a tentative report, which most likely is going to be safe when formulated to be nonirritating, but I'm going to bring up the issue of the 97 percent pure. What's the other 3 percent composition? And just see how Dan reacts to that, whether it got past his sniff test or not.

DR. HELDRETH: I just wanted to clarify. So the consensus currently is that there's not a dermal irritation issue, only potential ocular. Is that correct?

DR. MARKS: I need to go back and look at all the dermal irritation. I just put yes in that block, so I think it was more than eye.

DR. HELDRETH: Okay. Okay.

DR. MARKS: But I need to look at that.

DR. SLAGA: I thought it was only the eye. I didn't recall any dermal irritation. It was not an irritant in skin.

DR. MARKS: Okay. What page is that? I have under dermal irritation there were three in vitro, animal, and human. This is under dermal now. And I have that it was an irritant, so not only the eye but the skin, too.

DR. HELDRETH: Okay. I only brought it up because if it was only an ocular irritant, not a dermal irritant, we would often handle that in the discussion since ocular exposure would be incidental. But if it's also an irritant to the skin, then I withdraw.

DR. MARKS: Yeah. Look under page 16.

DR. HELDRETH: Okay.

DR. MARKS: The summary. And if you look at the third paragraph from the bottom, "Levulinic acid was determined to not be irritating in the epi skin assay. In a dermal irritation study in which Levulinic acid was applied full strength to intact or abraded rabbit skin for 24 hours under occlusion, moderate to severe irritation was observed. When it was diluted to 4 percent, it was not observed" -- irritation. So I guess it was -- and the use concentration is much less than 4 percent. So you get into do you set a range. And actually when I relook at that -- yeah. One could say it's not an irritant to the skin at the use concentration. Could you say that the same for the eye or not?

MS. RAJ: Well, I notice here, though, Dr. Marks and everyone, that on PDF page 14 the study where it was a moderate to severe irritant -- there are not many details in that study.

DR. MARKS: Right.

DR. SHANK: That study, the rabbit study was undiluted Levulinic acid.

DR. MARKS: Yes.

DR. SHANK: So I don't think that's relevant to cosmetic use.

MS. RAJ: Okay.

DR. SLAGA: I agree.

DR. MARKS: So Ron, would you just delete the irritation?

DR. SHANK: No. When formulated to be nonirritating because it is irritating to the eye.

DR. MARKS: Yeah. So just leave it formulate to be nonirritating. We don't have to be specific to say nonirritating to the eye. Yeah. I hear you. You can't hear me. Nonirritating -- yeah. So let's leave it like that for tomorrow. We're going to be seconding it. We'll see what the Belsito team -- and again, this is the first time we've seen this. So we'll have time to modify that in the next go round, which would be the draft final. Does that sound good?

DR. SHANK: Yes.

DR. MARKS: Lisa, Tom, Ron?

DR. SLAGA: Yeah.

DR. MARKS: Okay.

DR. SLAGA: Yes.

Full Panel – September 15, 2020

DR. BELSITO: Okay, Levulinic Acid and Sodium Levulinate, so this is the first time we're looking at the safety assessment of these two ingredients that function as skin-conditioning agents. Levulinic Acid is also reported as a fragrance ingredient, but as you know we don't look at those.

So, we got quite a bit of data. We looked at all of the data. However, we don't really have absorption and we don't have any DART data. So, we felt that this report at this point was insufficient for a 28-day dermal to clear DART.

We're also concerned because the ocular studies that were done neat would suggest that this is a relatively moderate to severe ocular irritant. And it turns out that the highest concentration of use, .5 percent, .57 percent is actually around the eye. So, we wanted some data on ocular irritation at concentration of use.

DR. BERGFELD: And that's a motion?

DR. BELSITO: That is our motion, yes.

DR. BERGFELD: Dr. Marks, do you want to comment or second?

DR. MARKS: I'll second that motion. And, we had one other concern with the insufficient data announcement. In the impurities and method of manufacture it says it's 97 percent pure. Lisa wanted to clarify what is the other three percent in the composition. And I love the way she stated this, if I have it correct, she wanted to see whether it passes Dan's sniff test.

DR. LIEBLER: I'm back; I crashed out for a few minutes. This is Levulinic?

DR. BERGFELD: Yes.

DR. LIEBLER: Impurities, you know I was okay with this for 97 percent. And, so I guess it did pass my sniff test. But, Lisa, do you want to elaborate?

DR. PETERSON: Well, so, you know, I'm new to this process and I've been learning and reading all of the minutes. On most of the chemicals you have always said, I'm not concerned, but it's not there, we should ask for it because just basically an i-dotting t-crossing. And, I think in this case because of the -- I think it was the method of manufacturing -- things start, you know, with chemical -- or, they isolated from organic, you know, things that come from algae or wood or other things that you know there could be a concern of metal contamination or something. And, I was told there is a boilerplate. But, I did notice that almost every time that there are no impurities listed, you say, oh, we need to have impurities. So, that's why I said it had to pass your sniff test.

DR. LIEBLER: Well played, Dr. Peterson; you're keeping me honest. I agree with you entirely.

DR. BELSITO: Well, I thought, Dan, yesterday we thought that based upon the method of manufacturing we didn't need the impurities.

DR. LIEBLER: I didn't hear the last part, method of manufacturing -- what?

DR. BELSITO: We discussed this in our team meeting and my question to you was do we need more of the impurities based upon the method of manufacturing, and I thought your answer was no.

DR. LIEBLER: Yeah, I think that -- I probably wouldn't have said anything if Lisa hadn't spoke up. I think she's got a good point about asking for this information. I mean, you know, honestly the method of manufacturing is reasonably straight forward, they list several steps, any and all of which could create impurities that could be relevant. So, let's go ahead and ask for it. I think Lisa's got a great point and we should ask.

DR. PETERSON: And part of the reason for pushing for it is that there's no method of purification. So, had there been a method of purification I would be less concerned. But there's no method of purification in the method of manufacturing, so that is probably why I'm hanging on to it and not letting go too.

DR. SNYDER: Yep.

DR. BELSITO: I mean, it's going out insufficient, so we can ask for it that's not an issue.

DR. SNYDER: Yep.

DR. BERGFELD: Any other discussion? It's been moved and second that we move forward with this as an IDA.

DR. BELSITO: Just to point out the penetration enhancer, so when and if we get to it that'll need to be in the discussion.

DR. BERGFELD: Anything else? I'm going to call the question then. All those not in favor of moving forward with this particular ingredient, please indicate by stating your name. I'll assume that the rest of you are voting for it, so it's unanimous report of IDA. We're moving on to the next ingredient, which is Dr. Marks' ingredient, Ubiquinone.

Safety Assessment of Levulinic Acid and Sodium Levulinate as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: February 16, 2021
Panel Meeting Date: March 11-12, 2021

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.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR.

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

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Levulinic Acid and Sodium Levulinate as used in cosmetic formulations. These ingredients are both reported to function as skin conditioning agents, while Levulinic Acid is also reported to function as a fragrance ingredient. The Panel reviewed relevant data relating to the safety of these ingredients in cosmetic formulations, and concluded….[to be determined].

INTRODUCTION

This is a safety assessment of Levulinic Acid and Sodium Levulinate, as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook (*wINCI; *Dictionary*), Levulinic Acid and Sodium Levulinate both are reported to function in cosmetics as skin conditioning agents; Levulinic Acid is also reported to function as a fragrance ingredient.[1]

Sodium Levulinate is the salt of Levulinic Acid. Upon dissociation in aqueous solution, these ingredients are identical. Thus, these ingredients are reviewed together in this report.

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 Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is provided on the Cosmetic Ingredient Review (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 was found on the European Chemicals Agency (ECHA) website.[2,3] Please note that 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. Data from a Research Institute for Fragrance Materials (RIFM) safety assessment of Levulinic Acid have also been included, and that assessment is cited when primary references were not available.[4]

CHEMISTRY

Definition and Structure

Levulinic Acid (CAS No. 123-76-2) is the organic acid that conforms to the structure depicted in Figure 1.[1] Levulinic Acid is a 5-carbon, oxocarboxylic, keto acid.[5]

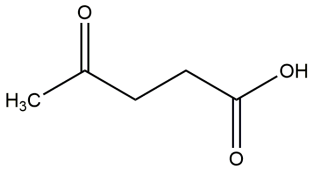


Figure 1. Levulinic Acid

Sodium Levulinate (CAS No. 19856-23-6) is the sodium salt of Levulinic Acid[1] that conforms to the structure depicted in Figure 2.

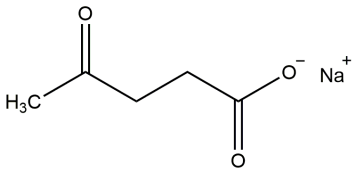


Figure 2. Sodium Levulinate

Chemical Properties

Levulinic Acid has a molecular weight of 116.11 g/mol and an estimated log K_{ow} of -0.498, while Sodium Levulinate has a formula weight of 138.1 g/mol and an estimated log K_{ow} of -0.616.[2,3,6,7] Levulinic Acid and Sodium Levulinate are both highly soluble in water and comprise carboxylic acid and ketone functional groups. While Sodium Levulinate is a solid, sodium salt, Levulinic Acid is a solid with a low melting point, which exhibits limited granularity.[2]

Ultraviolet-visible (UV/Vis) absorption spectra were obtained for Levulinic Acid.[4] No significant absorption was observed between 290 and 700 nm, and the corresponding molar absorption coefficient was well below the 1000 l/mol·cm

threshold for phototoxic effects. The chemical properties of Levulinic Acid and Sodium Levulinate are further outlined in Table 1.

Natural Occurrence

Levulinic Acid is found in both natural and processed foods, such as Chinese quince, papaya, rice, sake, and wheaten bread.[8]

Method of Manufacture

The following are general industrial methods of manufacture; it is unknown if these apply to the manufacture of cosmetic ingredients. Levulinic Acid can be produced from low grade cellulose,[9] sugar and starchy crops, wood, organic waste, or algae, as a hydrolysis and conversion step in the biorefinery process.[10] Sugars and starches are the most frequently used feedstock for mass production of Levulinic Acid and typically undergo a multi-step manufacturing process, including hydrolysis of polysaccharides with a Brønsted-Lowry acid (such as sulfuric acid) to yield hexose or pentose sugars (such as glucose), isomerization of glucose by a Lewis acid to yield fructose, dehydration of fructose to 5-(hydroxylmethyl)furfural (5-HMF) by a bifunctional acid,[5,9] and, lastly, rehydration of 5-HMF by a Brønsted-Lowry acid to yield Levulinic Acid.[10] Sodium salts, such as Sodium Levulinate, are typically derived from the reaction of the free acid (e.g., Levulinic Acid) with an inorganic base, such as sodium hydroxide.[1]

Impurities

The acceptance criteria for food-grade Levulinic Acid is no lower than 97% purity.[11] No further impurities data were found in the published literature, and unpublished data were not submitted.

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 ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2021 VCRP survey data, Levulinic Acid is reported to be used in 98 cosmetic formulations, and Sodium Levulinate is reported to be used in 295 cosmetic formulations, 206 of which are leave-on products (Table 2).[12] Results from the 2019 concentration of use survey, conducted by the Council, indicate that Levulinic Acid has the highest maximum concentration of use, at 4.5% in hair dyes, while Sodium Levulinate is used at a maximum concentration of 0.62% in mouthwashes and breath fresheners.[13] The greatest maximum concentrations for leave-on dermal exposure for each ingredient are in foundations containing Levulinic Acid (0.0005%) and eye shadows containing Sodium Levulinate (0.57%).

These ingredients have been reported to be used in products that may come into contact with the eyes; for example, Sodium Levulinate is reported to be used at up to 0.57% in eye shadows. The use of both ingredients in mouth freshening products, at a reported maximum concentration of 0.35% for Levulinic Acid and 0.62% for Sodium Levulinate, may lead to incidental ingestion and exposure to mucous membranes. Sodium Levulinate is reported to be used in baby products, at up to a 0.35% in baby lotion, oil, or cream formulations.

Additionally, Sodium Levulinate is reported to be used in 1 face powder formulation (concentration of use not reported), and, could therefore possibly be inhaled. 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.[14-16]

Both Levulinic Acid and Sodium Levulinate are not restricted from use in any way under the rules governing cosmetic products in the European Union.[17]

Non-Cosmetic

The bulk of Levulinic Acid use is as a chemical intermediate in the manufacture of biofuels and chemicals, fuel extenders, biodegradable polymers, plasticizers, herbicides, and antibiotics.[5,18]

In the US, Levulinic Acid is a food additive approved for human consumption as a flavoring agent and related substance, assuming good manufacturing practices and minimum use to achieve the desired effect. [21 CFR 172 § 515]. Levulinic Acid was included in the list of nonharmful artificial flavoring substances by the Council of Europe in 1974, at 50 ppm.[19] In 1999, the Joint Expert Committee on Food Additives (JECFA) deemed that Levulinic Acid posed no safety concerns.[20] Additionally, Levulinic Acid is proven to be effective in stunting bacterial growth in preserved, ready-to-eat meats and as a cytocidal agent in oral rinse solutions.[21-23]

Levulinic Acid appears on the FDA Inactive Ingredient List, and is listed as an inactive ingredient in the manufacturing of transdermal, extended release film and patches, with a maximum potency per unit dose of 16.5 mg and 20 mg, respectively.[24] Levulinic Acid has been investigated for its effectiveness in enhancing dermal penetration of drugs.[25]

TOXICOKINETIC STUDIES

Penetration Enhancement

Levulinic Acid

The performance of 3 transdermal buprenorphine patch formulations, combined with 8% (w/w) Levulinic Acid, lauryl alcohol, or Tween 80, was tested upon 1.5 cm x 1.5 cm of abdominal skin from male Sprague-Dawley rats (number not specified).[25] Response surface methodology was used to evaluate the interactive effects of various skin permeation and adhesion properties. The skin flux, and hence penetration potential of buprenorphine, was highest in the presence of Levulinic Acid. The authors postulated that the chemical structure of Levulinic Acid has the potential to disrupt or fluidize lipids in the stratum corneum, hence leading to an increased partitioning and absorption of buprenorphine.

Absorption, Distribution, Metabolism, and Excretion (ADME)

In Vitro

Sodium Levulinate

Livers isolated from male rats (number not specified) were used to observe the metabolism of [C_{1-5}-^{13}C] to 4-hydroxypentanoate in the presence and absence of ethanol.[26] The rat livers were perfused with 4 mM glucose and (i) nothing – the controls, (ii) 2 mM [C_{1-5}-^{13}C]levulinate, (iii) 2 mM levulinate + 20 mM ethanol, or (iv) 20 mM ethanol.[26] In contrast to metabolism observed in live rats, ethanol almost doubled the uptake of levulinate in the liver, and tripled the production of 4-hydroxypentanoate from levulinate in the isolated rat livers.

Animal

Intravenous

Sodium Levulinate

A study was conducted in rats to assess if Sodium Levulinate is metabolized to 4-hydroxypentanoate, and whether this process is accelerated in the presence of ethanol.[26] Twelve anesthetized male Sprague-Dawley rats were infused intravenously with a 150 mM solution of Sodium Levulinate at 12 µmol/min/kg for 2 h. Half of the rats dosed with Sodium Levulinate received an intraperitoneal bolus of 10% ethanol (1.7 M) in saline at 15 min in an amount calculated to achieve 10 mM ethanol concentration in the body. This bolus was then followed by a continuous intravenous 10% ethanol in saline infusion at 40 µmol/min/kg. The remaining six rats, dosed with Sodium Levulinate, were used as controls and were only infused with saline. Arterial blood was sampled every 20 min for 2 h. Compared to controls, rats infused with ethanol had significantly increased plasma levulinate and 4-hydroxypentanoate concentrations. The authors postulated that this incongruency is due to ethanol decreasing overall levulinate metabolism in vivo, in spite of stimulating the natural reduction of levulinate to 4-hydroxypentanoate.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Levulinic Acid

The acute dermal toxicity of Levulinic Acid was investigated following a single, semi-occlusive application to Sprague-Dawley rats, in accordance to Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 402.[2] Five male and 5 female rats were exposed to a single, undiluted dose of 2000 mg/kg and observed for mortality and clinical abnormalities for 15 d. No mortality and signs of toxicity were observed in either sex during the observation period, or at necropsy. Abnormalities at the treated site were absent as well. The acute dermal LD_{50} in rats was therefore determined to be > 2000 mg/kg. In rabbits, the acute dermal LD_{50} of Levulinic Acid was > 5000 mg/kg.[19] (Details were not provided.)

Oral

Levulinic Acid

The acute oral toxicity of Levulinic Acid was determined in female Sprague Dawley rats, using a single gavage exposure and 14-d observation, followed by necropsy.[2] Initially, 3 rats were dosed at 2000 mg/kg bw in distilled water. All 3 animals died the next day. Hunched posture, piloerection, and decreased activity were observed at the time of dosing. In a second group, 3 female animals were dosed at 300 mg/kg bw in distilled water. No deaths occurred and no signs of toxicity were seen at necropsy. A third group of 3 rats was also dosed at 300 mg/kg bw. No premature deaths occurred, and no signs

of toxicity were seen during the necropsy of these animals. No gross or clinical abnormalities were seen in animals that had prematurely died. It was determined that the oral LD_{50} is greater than 300 mg/kg bw, but lower than 2000 mg/kg bw.

In another study, the acute oral LD_{50} of Levulinic Acid in rats was determined to be 1850 mg/kg.[19] (Details were not provided.)

Short-Term Toxicity Studies

Animal

Oral

Levulinic Acid

In a short-term toxicity study, 3 groups of 3 rats were fed a diet with 0, 1, or 2% Levulinic Acid for 16 d.[27] No indications of toxicity were observed. (No further details provided.) Guinea pigs were used to investigate the short-term oral toxicity of Levulinic Acid.[27] The animals (number not specified) were given 0.5 to 5.0 ml of 10% Levulinic Acid per day (dosing duration not specified) by means of a 1-ml pipette, or a stomach tube. No gross abnormalities were observed upon necropsy.

Human

Oral

Levulinic Acid

Six healthy, human male adults ingested 3 ml of pure Levulinic Acid in 150 to 400 ml of fruit juice on a daily basis, with the exception of Sundays, for 30 d.[27] Clinical and laboratory testing of the resulting biological samples were taken prior to the test substance administration, after 2 wk of administration, and after 4 wk of administration. No significant or cumulative toxic effects were noted in the men, and the immediate hematological effects of the test substance on sugar, non-protein nitrogen, and creatine content were within expected ranges for ingestion of other ordinary foods.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

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

GENOTOXICITY

In Vitro

Levulinic Acid

In an Ames test, Levulinic Acid was evaluated, in accordance with OECD TG 471, using *Salmonella typhimurium* strains TA98, TA100, TA1537, and *Escherichia coli* strain WP2uvrA.[4] The strains were treated with Levulinic Acid, in water, at concentrations up to 5000 µg/plate. No increase in the mean number of revertant colonies was observed at any tested concentration in the presence or absence of S9 metabolism. (No further details provided.) Levulinic Acid was not considered mutagenic.

Levulinic Acid was assessed in the BlueScreen assay (i.e., a screening assay measuring genotoxic stress through human-derived gene expression).[4] Levulinic Acid was found positive for cytotoxicity without metabolic activation, and negative for genotoxicity, both with and without metabolic activation. (No further details provided.)

A chromosomal aberration assay was performed (with and without metabolic activation) in cultured human lymphocytes, in accordance with OECD TG 473, to determine the clastogenic potential of Levulinic Acid.[2,4] Three treatment series were included in the study. The cells underwent a short, 3-h treatment with the test substance at concentrations up to 1160 µg/ml in dimethyl sulfoxide (DMSO), both in the absence and presence of metabolic activation. A long-term, continuous treatment followed with the test substance at concentrations up to 580 µg/ml, only in the absence of metabolic activation, until harvest at 24 h. Appropriate negative and positive controls were included. Following treatment with the test substance, no statistically significant increases in the incidence of cellular aberrations were observed.

Levulinic Acid was further examined for mutagenic activity by assaying for the induction of 6-thioguanine resistant mutants in Chinese hamster lung fibroblast V79 cells after in vitro treatment, according to OECD TG 476.[2] A main assay was performed in the absence and presence of S9 metabolism. The test substance was assayed at concentrations of 36.3, 72.5, 145, 290, 580, and 1160 µg/ml. No relevant toxicity was observed at any concentration tested, in the absence or presence of S9 metabolism. It was therefore determined that the test substance does not induce genetic mutation in Chinese hamster V79 cells, under the reported experimental conditions.

CARCINOGENICITY STUDIES

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

DERMAL IRRITATION AND SENSITIZATION

Irritation

In Vitro

Levulinic Acid

A study to investigate the skin irritation potential of Levulinic Acid was conducted using a reconstructed human epidermis (RhE) model, EPISKIN™, in accordance with OECD TG 439.[2] The test substance, as well as controls, were tested for their ability to impair cell viability after an exposure of 15 min followed by a 42 ± 1 h recovery period. Twenty µl of the test substance, or negative/positive control, was placed in each well. The colorimetric measurement of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction was used as an index of cell viability. Results from the blank, negative, and positive controls were as deemed acceptable. The test substance was determined to not be irritating, based upon the measured cell viability above the 60% threshold for skin irritation potential (i.e., 62%).

Animal

Levulinic Acid

In a dermal irritation study, Levulinic Acid was applied undiluted to intact or abraded rabbit skin for 24 h, under occlusion.[19] The occlusive exposure of Levulinic Acid was moderately to severely irritating to rabbit skin. (No other details were provided.)

Human

Levulinic Acid

Levulinic Acid was tested for dermal irritation potential in humans at 4% in petrolatum using a 48-h occlusive patch.[19] No irritation was observed. (No other details were provided.)

Sensitization

In Vitro

Sodium Levulinate

The sensitizing potential of Sodium Levulinate was evaluated using the human cell line activation test (h-CLAT), in accordance to OECD TG 442E.[3] Human monocytic cells (THP-1) were exposed to eight concentrations of the test substance ranging from 39.1 to 5000 µg/ml in RPMI (Roswell Park Memorial Institute) growth medium for 24 h. Post-exposure, the expression of two cell surface antigens, CD86 and CD54, was measured by flow cytometry; vehicle control (RPMI), negative control (lactic acid), and positive controls (2,4-dinitrochlorobenzene or nickel sulfate) were also run in parallel. The measured relative fluorescence intensities (RFI) of CD86 and CD54 remained lower than the test positive criteria of ≥200% for CD54 and ≥ 150% for CH86, between concentrations of 39.1 to 2500 µg/ml. RFI values, however, were higher than 200% and 150% at 5000 µg/ml, indicating the potential of the test substance as a sensitizer at higher doses.

Animal

Levulinic Acid

The ability of Levulinic Acid to induce skin sensitization in female CBA/JN mice was evaluated using the local lymph node assay (LLNA) according to the OECD TG 442b.[2] The test item was topically administered at concentrations of 5, 10, or 25% (w/w), in a 4:1 ratio of acetone:olive oil, for 3 d. Vehicle controls (13 - 19 animals) received acetone and olive oil mixture, while test animals received topical applications of Levulinic Acid at 5% (21 - 27 animals), 10% (29 - 35 animals), or 25% (37 - 43 animals). The positive control group (31 - 45 animals) received 25% (w/w) α-hexylcinnamaldehyde, in a 4:1 ratio of acetone and olive oil. After 1 d of no treatment, bromodeoxyuridine /5-bromo-2'-deoxyuridine (BrdU) solution was injected intraperitoneally. One d after the BrdU injection, the animals were killed, auricular lymph nodes were rapidly excised, and cell suspensions were prepared for the evaluation of lymph node proliferation. An increase in the cell proliferation of draining lymph nodes was observed in the low, medium, and high dose groups with a stimulation index (SI) of 1.31, 1.88, and 2.05, respectively, and a statistically significant difference between both the mid- and high dose groups with the negative control group was observed.

Human

Levulinic Acid

A human skin maximization test was conducted on 26 subjects.[19] The test substance was tested at a concentration of 4% in petrolatum and produced no sensitization reactions. (No further details provided).

Sodium Levulinate

A product containing 0.4011% Sodium Levulinate was tested in a human repeated insult patch test (HRIPT) in 103 subjects.[28] The test material (approximately 25-38 mg/cm^2) was applied to the back via nine, occlusive, 24-h induction applications, made over a 3-wk induction period; induction sites were scored 24 and 48 h after patch removal. After a 2-wk non-treatment period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and the reactions were scored on a scale of 0-4, at 24 and 72 h after application. No signs of irritation or sensitization were observed during induction or challenge; the researchers concluded that the test material did not induce dermal sensitization.

In a separate HRIPT, a product containing 0.57% Sodium Levulinate was tested in 53 subjects, following the same procedure described above.[29] No signs of irritation or sensitization were observed during induction or challenge; the researchers concluded that the test material did not induce dermal sensitization.

OCULAR IRRITATION STUDIES

In Vitro

Levulinic Acid

The potential of Levulinic Acid to cause ocular irritation was investigated in a human cornea model, EpiOcular™ eye irritation test, according to the OECD TG 492.[2] Fifty µl of the test substance was applied to three-dimensional human cornea tissue, in duplicate, for an exposure time of 30 min. After treatment, the test substance was rinsed, and tissue cell viability was evaluated by an MTT assay. Demineralized water and methyl acetate were tested concurrently as negative and positive controls, respectively. The mean tissue viability was found to be 2.5%, which is well below the threshold for irritation potential (≤ 60%). The test substance was considered an eye irritant and capable of inducing serious eye damage.

In accordance with OECD TG 437, Levulinic Acid was further evaluated for the potential for ocular irritancy in a bovine corneal opacity and permeability (BCOP) assay.[2] Using the "closed chamber-method," 750 µl of the negative control, Hank's Balanced Salt Solution, positive control, dimethylformamide, or the test substance were pipetted on to the cornea, which had been incubated with Eagle's medium without phenol red at 32 ± 1°C for 1 h. The test substance was incubated on the cornea for 10 min at 32 ± 1ºC. Post-removal of the test substance and 2 h post-incubation, corneal opacity and permeability values were measured. The calculated in vitro irritancy score (IVIS) was 84.29, which is within the range for classification for a substance causing serious eye damage.

SUMMARY

This report addresses the safety of Levulinic Acid and Sodium Levulinate, a carboxylic acid and its salt. According to the *Dictionary*, Levulinic Acid and Sodium Levulinate are reported to function as skin conditioning agents in cosmetics, while Levulinic Acid is also a fragrance ingredient. In 2021, Levulinic Acid is reported to be used in 98 cosmetic formulations, and Sodium Levulinate is reported to be used in 295 cosmetic formulations. According to 2019 concentration of use data obtained by the Council, the highest concentration of use of Levulinic Acid is in hair dyes, at 4.5%, and the highest concentration of use of Sodium Levulinate is in mouthwashes and breath fresheners at 0.62%. The highest reported concentration of use in a leave-on formulation for Sodium Levulinate is 0.57% in eye shadows. Both Levulinic Acid and Sodium Levulinate are used in products which involve dermal and mucous membrane contact, and Sodium Levulinate could possibly be inhaled, as it is used in a face powder formulation. Non-cosmetic uses include manufacturing of biofuels, chemicals, fuel extenders, plasticizers, pharmaceuticals, food additives and flavoring, and as inactive ingredients in approved drugs.

Three transdermal buprenorphine patch formulations were tested for penetration using 8% (w/w) Levulinic Acid, lauryl alcohol, or Tween 80. The penetration potential of buprenorphine was highest in the presence of Levulinic Acid.

Isolated male rat livers were used to observe the metabolism of Levulinic Acid to 4-hydroxypentanoate in the absence and presence of ethanol. Ethanol almost doubled the uptake of levulinate, and tripled the production of 4-hydroxypentanoate from levulinate in the isolated rat livers.

Anesthetized male Sprague-Dawley rats were infused intravenously with a 150 mM solution of Sodium Levulinate at 12 µmol/min/kg for 2 h. Half of these rats then received an intraperitoneal bolus of 10% ethanol 15 min after the exposure to Sodium Levulinate, while the other half only received saline (control). Compared to controls, the rats infused with ethanol had significantly increased plasma levulinate and 4-hydroxypentanoate concentrations.

The acute dermal LD_{50} of a semi-occlusive application of Levulinic Acid in Sprague-Dawley rats was determined to be > 2000 mg/kg. The acute dermal LD_{50} in rabbits exceeded 5000 mg/kg.

In an acute toxicity study, female Sprague-Dawley rats were dosed by gavage with Levulinic Acid. Animals dosed with 2000 mg/kg bw died the following day. After 2 groups of 3 rats were dosed with 300 mg/kg bw without dying prematurely

or showing signs of toxicity, the acute toxicity estimate was determined to be greater than 300 mg/kg bw, but lower than 2000 mg/kg bw. In another study, the acute oral LD_{50} of Levulinic Acid in rats was determined to be 1850 mg/kg.

In short-term oral toxicity studies with Levulinic Acid, no signs of toxicity or gross abnormalities were observed in rats fed a 16-d diet with up to 2% Levulinic Acid, or guinea pigs dosed with up to 10% Levulinic Acid. Similarly, in humans, no significant immediate or cumulative toxic effects were observed when 6 male subjects ingested 3 ml of Levulinic Acid daily in fruit juice over the course of 4 wk.

In an Ames test, Levulinic Acid was evaluated at concentrations up to 5000 µg/plate in *S. typhimurium* strains TA98, TA100, TA1537, and *E. coli* WP2uvrA strains. No increase in revertant colonies was observed in the presence or absence of metabolic activation. Levulinic Acid was determined to be non-mutagenic. In a BlueScreen assay, Levulinic Acid was found positive for cytotoxicity without metabolic activation, and negative for genotoxicity, both with and without metabolic activation. Levulinic Acid was assayed at up to 1160 µg/ml to test its ability to induce chromosomal damage in cultured human lymphocytes, and 6-thioguanine resistant mutants in Chinese hamster V79 cells, in the presence and absence of metabolic activation. No toxicity was observed in either study at any concentration tested, in the presence or absence metabolic activation.

Levulinic Acid was determined to not be irritating in the EPISKIN™ assay. In a dermal irritation study in which Levulinic Acid was applied full strength to intact or abraded rabbit skin for 24 h under occlusion, moderate to severe irritation was observed. When Levulinic Acid was tested at 4% in petrolatum in a 48-h occlusive patch test in humans, no irritation was observed.

The sensitizing potential of Sodium Levulinate was evaluated using the h-CLAT, and the test substance was identified as a potential sensitizer at the highest tested concentration of 5000 µg/ml. In an LLNA, evaluating Levulinic Acid at 5, 10, and 25% (w/w), statistically significant differences between the SI values of the mid- and high-dose groups, compared to the negative control group, were observed. In a human skin maximization test, 26 volunteers were exposed to 4% Levulinic Acid in petrolatum. No sensitization reactions occurred. In two separate HRIPTs, evaluating products containing 0.4011% and 0.57% Sodium Levulinate, no signs of irritation or sensitization were observed during induction or challenge; the test materials were deemed non-sensitizers.

Levulinic Acid was determined to be a potential ocular irritant, based on the results obtained in an EpiOcular™ assay. Levulinic Acid was further evaluated in a BCOP assay, and the calculated in vitro irritancy score was within the range of causing serious eye damage.

DRAFT DISCUSSION

[*Please note, this discussion is in draft form and will most likely modified following the meeting.]*

Levulinic Acid and Sodium Levulinate are essentially identical in aqueous solution, and are, therefore, being reviewed together in this assessment.

The Panel recognized that these ingredients can enhance the penetration of other ingredients through the skin, as seen in the aforementioned study of transdermal buprenorphine patch performance. The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

The Panel discussed the issue of incidental inhalation exposure from powder products. VCRP data indicate that Sodium Levulinate is being used in a face powder formulation; however, concentration of use data were not available. Droplets/particles deposited in the nasopharyngeal or bronchial 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 concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

CONCLUSION

To be determined.

TABLES

Table 1. Chemical properties of Levulinic Acid and Sodium Levulinate

Property	Value	Reference
Levulinic Acid		
Physical Form (@ 20°C & 1013 hPa)	solid	2
Color	white-pale yellow	2
Molecular Weight (g/mol)	116.11	6
Density/Specific Gravity (@ 20 °C)	1.1398	2
Topological Polar Surface Area (Å^2)	54.4	6
Vapor pressure (mmHg @ 20ºC; 25°C)	0.00281; 0.00464	2
Melting Point (ºC)	27.21 - 29.56	2
Boiling Point (ºC)	251.70 - 252.20	2
Water Solubility (g/l @ 20ºC & pH = 1)	791.3	2
Ethanol Solubility	very soluble	2
log K_{ow} (@ pH = 2 & 20ºC)	-0.498 (estimated)	2
Disassociation constant pKa (@ 20ºC)	4.62	2
Sodium Levulinate		
Physical Form (@ 20°C & 1013 hPa)	solid, powder	3
Color	white- off-white	3
Formula Weight (g/mol)	138.1	7
Density/Specific Gravity (@ 20ºC)	1.4795g/ml	3
Topological Polar Surface Area (Å^2)	57.2	7
Particle size Distribution (D_{50}; µm)	154.7	
Vapor pressure (mmHg @ 135ºC)	0.000139	3
Melting Point (ºC)	170.2	3
Boiling Point (ºC)	not observed; decomposition > 274.6	3
Water Solubility (g/l @ 20ºC & pH = 8)	797.2	3
log K_{ow} (@ pH = 2 & 20ºC)	-0.616 (estimated)	3
Disassociation constant pKa	9.38	3

Table 2. Frequency of use (2021)[12] and concentration of use (2019)[13] data, according to duration and type of exposure

	# of Uses[12]	Max Conc of Use (%)[13]	# of Uses[12]	Max Conc of Use (%)[13]
	Levulinic Acid		Sodium Levulinate	
Totals*	**98**	**0.0005-4.5**	**295**	**0.0005-0.62**
Duration of Use				
Leave-On	*78*	*0.0005*	*206*	*0.0005-0.57*
Rinse-Off	*20*	*0.2-4.5*	*72*	*0.18-0.62*
Diluted for (Bath) Use	*NR*	*NR*	*17*	*NR*
Exposure Type				
Eye Area	27	NR	36	0.57
Incidental Ingestion	NR	0.2-0.35	NR	0.18-0.62
Incidental Inhalation-Spray	15[a]; 20[b]	0.2-0.35[a]	75[a]; 61[b]	0.18-0.62[a]
Incidental Inhalation-Powder	20[b]	NR	1; 61[b]; 2[c]	0.002-0.0072[c]
Dermal Contact	93	0.0005	287	0.0005-0.57
Deodorant (underarm)	NR	NR	1[a]	NR
Hair - Non-Coloring	5	0.48	8	NR
Hair-Coloring	NR	4.5	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	3	0.2-0.35	60	0.18-0.62
Baby Products	NR	NR	3	0.35

*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
NR – no reported use

REFERENCES

1. Nikitakis J, Kowcz A. wINCI: *International Cosmetic Ingredient Dictionary and Handbook.* http://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, DC: Personal Care Products Council. Last Updated: Accessed: January 23, 2020.

2. European Chemical Agency(ECHA). REACH registration dossier: 4-oxovaleric acid (CAS 123-76-2). https://echa.europa.eu/registration-dossier/-/registered-dossier/17335/. Last Updated: 2019. Accessed: 10/30/2019.

3. European Chemical Agency(ECHA). REACH registration dossier: Sodium-4-oxovalerate (CAS 19856-23-6). https://echa.europa.eu/registration-dossier/-/registered-dossier/23640/. Last Updated: 2019. Accessed: 10/30/2019.

4. Api AM, Belmonte F, Belsito D, et al. RIFM fragrance ingredient safety assessment, levulinic acid, CAS Registry Number 123-76-2 (published online ahead of print). *Food Chem Toxicol* 2020:111111.

5. Stottmeister U, Aurich A, Wilde H, Andersch J, Schmidt S, Sicker D. White biotechnology for green chemistry: fermentative 2-oxocarboxylic acids as novel building blocks for subsequent chemical syntheses. *J Ind Microbiol Biotechnol* 2005;32(11-12):651-664.

6. National Library of Medicine. PubChem : Levulinic Acid (Compound). https://pubchem.ncbi.nlm.nih.gov/compound/11579#section=Chemical-and-Physical-Properties. Last Updated: 2019 Jan 8. Accessed: 10/30/2019.

7. National Library of Medicine. PubChem : Sodium Levulinate (Compound). https://pubchem.ncbi.nlm.nih.gov/compound/Sodium-levulinate#section=Chemical-and-Physical-Properties. Last Updated: 2019 Jan 8. Accessed: 10/30/2019.

8. Nijssen LM, Ingen-Visscher CAv, Donders JJH. VCF Volatile Compounds in Food: database.1963-2018.

9. O'Neil MJ (ed). *The Merck Index: an Encyclopedia of Chemicals, Drugs, and Biologics.* 15th ed. Cambridge, UK.: Royal Society of Chemistry; 2013.

10. Signoretto M, Taghavi S, Ghedini E, Menegazzo F. Catalytic Production of Levulinic Acid (LA) from Actual Biomass. *Molecules* 2019;24(15):2760.

11. Council of Experts, United States Pharmacopeial Convention. Food Chemicals Codex, 12th ed. (Online). United States Pharmacopeia. www.foodchemicalscodex.org. Accessed. 08/10/2020.

12. U.S.Food and Drug Administration (FDA). U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD. 2021. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2021; received January 21, 2021.)

13. Personal Care Products Council. 2019. Concentration of Use by FDA Product Category: Levulinic Acid and Sodium Levulinate. (Unpublished data submitted by Personal Care Products Council on January 31, 2019.)

14. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). 2015. Cosmetic Powder Exposure. (Unpublished data submitted by the Personal Care Products Council on November 3, 2015.)

15. Aylott R, Byrne G, Middleton J, Roberts M. Normal use levels of respirable cosmetic talc: preliminary study. *Int J Cosmet Sci* 1979;1(3):177-186.

16. Russell R, Merz R, Sherman W, Sivertson J. The determination of respirable particles in talcum powder. *Food Cosmet Toxicol* 1979;17(2):117-122.

17. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. http://ec.europa.eu/growth/tools-databases/cosing/. Last Updated: 2016. Accessed: 11/1/2019.

18. Hachuta B, Polasz A, Dzida M, Nowak M, Kusz J, eds. *Acta Crystallogr Sect E Struc Rep Online.* 2013. Levulinic Acid; No. 69(Pt. 9): 01406.

19. Anonymous. Laevulinic Acid. *Food Cosmet Toxicol* 1979;17:847-848.

20. Joint FAO/WHO Expert Committe on Food Additives. Evaluation of certain food additives and contaminants: fifty-third report of the Joint FAO/WHO Expert Committee on Food Additives (WHO technical report series; 896). Rome, Italy1999. https://apps.who.int/iris/bitstream/handle/10665/42378/WHO_TRS_896.pdf;jsessionid=A612B287CAA3CFEF205AA4CEC6DB50F9?sequence=1. Accessed 10/30/2019.

21. Carpenter CE, Smith JV, Broadbent JR. Efficacy of washing meat surfaces with 2% levulinic, acetic, or lactic acid for pathogen decontamination and residual growth inhibition. *Meat Sci* 2011;88(2):256-260.

22. Thompson RL, Carpenter CE, Martini S, Broadbent JR. Control of Listeria monocytogenes in ready-to-eat meats containing sodium levulinate, sodium lactate, or a combination of sodium lactate and sodium diacetate. *J Food Sci* 2008;73(5):M239-244.

23. Wang BY, Hong J, Ciancio SG, Zhao T, Doyle MP. A novel formulation effective in killing oral biofilm bacteria. *J Int Acad Periodontol* 2012;14(3):56-61.

24. US Food and Drug Administration (FDA) Department of Health and Human Services. Inactive Ingredient Search for Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Last Updated: 2020. Accessed: 10/15/2019.

25. Taghizadeh SM, Moghimi-Ardakani A, Mohamadnia F. A statistical experimental design approach to evaluate the influence of various penetration enhancers on transdermal drug delivery of buprenorphine. *J Adv Res* 2015;6(2):155-162.

26. Harris SR, Zhang GF, Sadhukhan S, et al. Metabolism of levulinate in perfused rat livers and live rats: conversion to the drug of abuse 4-hydroxypentanoate. *J Biol Chem* 2011;286(7):5895-5904.

27. Tischer R, Fellers C, Doyle B. The Nontoxicity of Levulinic Acid. *J Am Pharm Assoc,* 1942;31:217-220.

28. Essex Testing Clinic, Inc. 2016. Clinical safety evaluation repeated insult patch test (product containing 0.4011% Sodium Levulinate). (Unpublished data submitted by the Personal Care Products Council on March 2, 2020.)

29. Essex Testing Clinic, Inc. 2016. Clinical safety evaluation repeated insult patch test (product containing 0.57% Sodium Levulinate). (Unpublished data submitted by the Personal Care Products Council on March 2, 2020.)

2021 VCRP (FDA) Frequency of Use Data

Levulinic Acid Total: 98

INGREDIENT_NAME	CATEGORY	CPIS_COUNT
LEVULINIC ACID	03C -Eye Shadow	22
LEVULINIC ACID	03D - Eye Lotion	5
LEVULINIC ACID	05A -Hair Conditioner	2
LEVULINIC ACID	05F - Shampoos (non-coloring)	2
LEVULINIC ACID	05I - Other Hair Preparations	1
LEVULINIC ACID	07A - Blushers (all types)	1
LEVULINIC ACID	07I - Other Makeup Preparations	8
LEVULINIC ACID	10E - Other Personal Cleanliness Products	3
LEVULINIC ACID	12A - Cleansing	12
LEVULINIC ACID	12C - Face and Neck (exc shave)	15
LEVULINIC ACID	12D - Body and Hand (exc shave)	5
LEVULINIC ACID	12F - Moisturizing	10
LEVULINIC ACID	12G - Night	4
LEVULINIC ACID	12H - Paste Masks (mud packs)	1
LEVULINIC ACID	12I - Skin Fresheners	1
LEVULINIC ACID	12J - Other Skin Care Preps	6

Sodium Levulinate Total: 295

SODIUM LEVULINATE	01B - Baby Lotions, Oils, Powders, and Creams	2
SODIUM LEVULINATE	01C - Other Baby Products	1
SODIUM LEVULINATE	02A - Bath Oils, Tablets, and Salts	5
SODIUM LEVULINATE	02B - Bubble Baths	12
SODIUM LEVULINATE	03C - Eye Shadow	22
SODIUM LEVULINATE	03D - Eye Lotion	11
SODIUM LEVULINATE	03E - Eye Makeup Remover	1
SODIUM LEVULINATE	03G - Other Eye Makeup Preparations	2
SODIUM LEVULINATE	05A - Hair Conditioner	2
SODIUM LEVULINATE	05F - Shampoos (non-coloring)	5
SODIUM LEVULINATE	05I - Other Hair Preparations	1
SODIUM LEVULINATE	07A - Blushers (all types)	3
SODIUM LEVULINATE	07B - Face Powders	1
SODIUM LEVULINATE	07C - Foundations	1
SODIUM LEVULINATE	07I - Other Makeup Preparations	7
SODIUM LEVULINATE	10A - Bath Soaps and Detergents	29
SODIUM LEVULINATE	10B - Deodorants (underarm)	1
SODIUM LEVULINATE	10E - Other Personal Cleanliness Products	14
SODIUM LEVULINATE	11E - Shaving Cream	1
SODIUM LEVULINATE	12A - Cleansing	19
SODIUM LEVULINATE	12C - Face and Neck (exc shave)	39
SODIUM LEVULINATE	12D - Body and Hand (exc shave)	22
SODIUM LEVULINATE	12F - Moisturizing	56
SODIUM LEVULINATE	12G - Night	7
SODIUM LEVULINATE	12H - Paste Masks (mud packs)	1
SODIUM LEVULINATE	12I - Skin Fresheners	11
SODIUM LEVULINATE	12J - Other Skin Care Preps	18
SODIUM LEVULINATE	13A - Suntan Gels, Creams, and Liquids	1