Safety Assessment of Glycolactones as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	September 1, 2022
Panel Meeting Date:	September 26 – 27, 2022

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.; 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 members involved in this assessment: Lisa A. Peterson, Ph.D. and Ronald C. Shank, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Senior Scientific Analyst/Writer, CIR.

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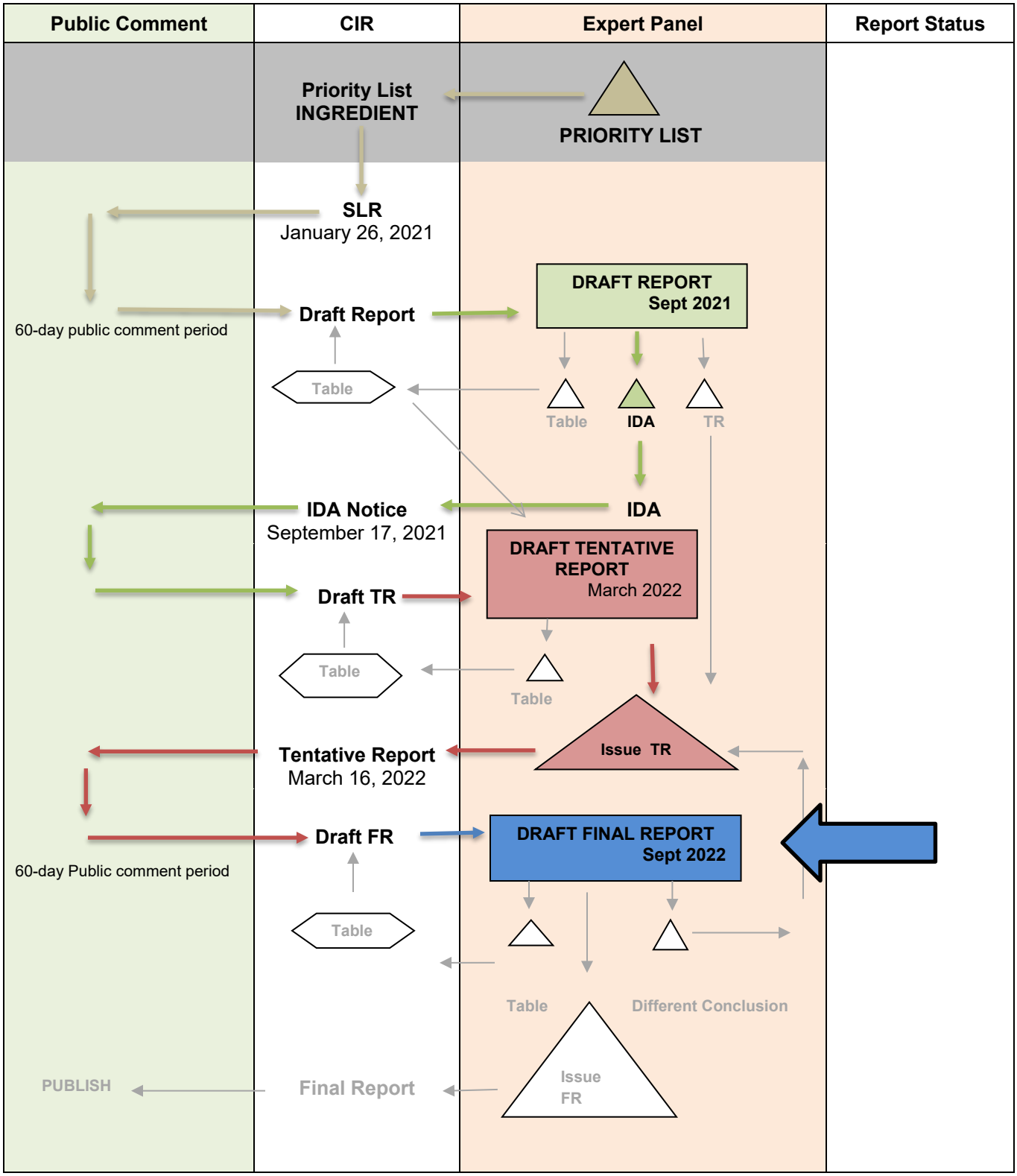
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Glycolactones

MEETING September 2022



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Senior Scientific Analyst/Writer, CIR
Date: September 1, 2022
Subject: Safety Assessment of Glycolactones as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of Glycolactones as Used in Cosmetics (*report_Glycolactones_092022*). At the March 2022 meeting, the Expert Panel for Cosmetic Ingredient Safety (Panel) issued a Tentative Report for public comment with the conclusion that Gluconolactone is safe as used in cosmetics in the present practices of use and concentration as described in the safety assessment. The Panel also concluded that the available data are insufficient to make a determination that the remaining ingredients (i.e., Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone, none of which are reported to be in use) are safe under the intended conditions of use in cosmetic formulations. To conclude on the safety, the Panel requires impurities data for these ingredients, and cosmetic-specific method of manufacturing data for Glucarolactone and Glucoheptonolactone.

Since the issuing of the tentative report, no unpublished data have been received. Comments on the tentative report that were received from the Council (*PCPCcomments_Glycolactones_092022*) have been addressed. A comments response checklist is included (*response-PCPCcomments_Glycolactones_092022*).

Also included in this packet are the report history (*history_Glycolactones_092022*), data profile (*dataprofile_Glycolactones_092022*), search strategy (*search_Glycolactones_092022*), transcripts of the previous meeting (*transcripts_Glycolactones_092022*), 2022 VCRP data (VCRP_*Glycolactones_092022)*, and flow chart (*flow_Glycolactones_092022*).

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: April 4, 2022

SUBJECT: Tentative Report: Safety Assessment of Glycolactones as Used in Cosmetics (release date March 16, 2022)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Glycolactones as Used in Cosmetics.

Abstract – Please correct: "however, the concluded the available data are insufficient" (add "Panel")

Definition and Structure – If "Figure 1" is stated in the text, the figure should be labeled.

ADME, Human – The secondary source (reference 22) indicates that the primary reference for the human oral study is: Chenoweth, M. B., Civin, H., Salzman, C., Cohn, M. & Gold, H. (1941) J. Lab. Clin. Med., 26, 1574.
Was there any attempt to obtain this study? Rather than stating that "No other details regarding this study were provided", it would be helpful to note that the primary reference was published in 1941, and that "No other details regarding this study were identified" (or "available").

Chronic – Please correct: "Frequency and severity of this effects increased with dose." (delete "s")

Discussion – The Discussion states that the data are not sufficient to support "read-across" from Gluconolactone, and only lists impurities and method of manufacture information as the data needs. This suggests that read-across from Gluconolactone for the safety data is considered acceptable. If this is true, it would be helpful if that was clearly stated in the Discussion. If the determination of "read-across" for the safety data can only be completed if impurities information is available for the other ingredients, the Discussion should be revised to make this clear.

Table 5 – As this table is only on one ingredient, for the final report, Gluconolactone should be added to the title of the table and the Test Article column should be deleted.

Glycolactones - September 2022 meeting – Priya Cherian	
Comment Submitter: Personal Care Products Council **Date of Submission: April 4, 2022**	
Comment	**Response/Action**
Abstract – Please correct: "however, the concluded the available data are insufficient" (add "Panel")	Addressed
Definition and Structure – If "Figure 1" is stated in the text, the figure should be labeled.	Addressed
ADME, Human – The secondary source (reference 22) indicates that the primary reference for the human oral study is: Chenoweth, M. B., Civin, H., Salzman, C., Cohn, M. & Gold, H. (1941) J. Lab. Clin. Med., 26, 1574. Was there any attempt to obtain this study? Rather than stating that "No other details regarding this study were provided", it would be helpful to note that the primary reference was published in 1941, and that "No other details regarding this study were identified" (or "available").	This study has been removed from the report as the test substance used, according to the original reference, is gluconic acid
Chronic – Please correct: "Frequency and severity of this effects increased with dose." (delete "s")	Addressed
Discussion – The Discussion states that the data are not sufficient to support "read-across" from Gluconolactone, and only lists impurities and method of manufacture information as the data needs. This suggests that read-across from Gluconolactone for the safety data is considered acceptable. If this is true, it would be helpful if that was clearly stated in the Discussion. If the determination of "read-across" for the safety data can only be completed if impurities information is available for the other ingredients, the Discussion should be revised to make this clear.	Addressed – the following statement has been removed from the Discussion: "However, although the ingredients in this group are chemically similar, the Panel did not have sufficient data to support read-across from Gluconolactone to the other ingredients in this report."
Table 5 – As this table is only on one ingredient, for the final report, Gluconolactone should be added to the title of the table and the Test Article column should be deleted	Addressed

Glycolactones – History

February 2020
-2020 VCRP data received for Gluconolactone

April 2020
-concentration data received from Council for Gluconolactone

October 2020
-SLR issued

January 2021
-updated 2021 VCRP data received for Gluconolactone

February 2021
-comments on SLR received
-unpublished data received: HRIPT on product containing 1.4850% Gluconolactone
-unpublished data received: HRIPT on product containing 0.041625% Gluconolactone

June 2021
-unpublished data received: in vitro ocular and dermal irritation summary data on Gluconolactone

September 2021
-Expert Panel reviews Draft Report and issues an IDA with the following data requests:
    -Method of manufacturing data for Glucarolactone and Glucoheptonolactone
    -Impurities data on Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone
    -Irritation and Sensitization data for Gluconolactone at maximum concentrations of use
-Comments on Draft Report received
-Unpublished data received: HRIPT on a product containing 15% Gluconolactone

January 2022
-Updated 2022 VCRP data received
    -Gluconolactone is still only ingredient in use, number of uses increased

March 2022
-Panel reviews Draft Tentative Report and determines a split conclusion:
    -safe as used conclusion for Gluconolactone
    -insufficient data for Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone – insufficiencies include method of manufacturing and/or impurities data
-Tentative Report posted for public response

April 2022
-Comments received from Council on Tentative Report

September 2022
-Panel reviews Draft Final Report

Glycolactones Data Profile – September 2022 – Priya Cherian																															
				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
Galactonolactone		X		X																									
Glucarolactone				X																									
Glucoheptonolactone				X																									
Gluconolactone	X	X	X	X		X		X			X			X	X	X		X			X			X		X		X	
Ribonolactone		X		X																									

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

Glycolactones – September 2022 - Priya Cherian

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Gluconolactone	90-80-2	Y	Y	N	Y	Y	Y	N	Y	N	N	N	Y	N	N	N	N	N	Y
Galactonolactone	1668-08-2 (L-); 2782-07-2 (D-)	Y	Y	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y
Glucarolactone	2782-04-9; 389-36-6	Y	Y	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y
Glucoheptanolactone	60046-25-5	Y	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y
Ribonolactone	5336-08-3	Y	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y

Y = yes/data found; N = no/data not found

Search Strategy

- All search terms were used in PubMed and ToxNet
- INCI names and CAS numbers were searched in the "Pertinent Websites" listed below

Typical Search Terms

- INCI names
- CAS numbers
- chemical/technical names
- Search terms:
  - Allergy
  - Sensitization
  - Irritation
  - Metabolism
  - Manufacturing
  - Production
  - Synthesis
  - Clinical
  - Reproduction
  - Inhalation
  - Maternal
  - Ocular
  - Eye
  - Dermal
  - Cosmetic
  - Respiratory
  - Dermal Penetration
  - Absorption
  - Toxicity
  - Carcinogenicity
  - Mutagenicity

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

SEPTEMBER 2021 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – September 13, 2021

DR. BELSITO: Okay. And then we're moving on to the Glycolactones. Okay, so it's the first time that we're looking at these since the SLR was released. We got data from Council in the draft report. In vitro dermal irritation assays, the 70 to 80 percent gluconolactone, HRIPTs on 100 or more subjects using a cream with 0.04 percent or in a product containing 1.485 percent. But it's used up to 15 percent in leave-ons. We've got some in vitro ocular irritation.

Total uses 262 formulations, 173 leave-ons. Best max concentration of use, like I said, 15 percent. There were ingredients not in use: Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone. So where are we on these lactones?

DR. LIEBLER: I thought that they're insufficient for method of manufacture and impurities for anything but Gluconolactone, or at least the impurities. All we've got is Gluconolactone. It doesn't really cover the others. We do have a method of manufacture for Galactonolactone and Gluconolactone. I have the description of synthesis for Ribonolactone but no impurities.

DR. BELSITO: Yeah, so I had insufficient (audio gap) manufacturing for Glucarolactone and Glucoheptonolactone. Is that what you said, Dan?

DR. LIEBLER: Correct.

DR. BELSITO: And impurities I had for all except Gluconolactone.

DR. LIEBLER: That's right.

DR. BELSITO: Okay, and then I thought we probably needed sensitization at max concentration of use at 20 percent.

DR. LIEBLER: I thought it was 15. Anyway, whatever max is. Yes.

DR. BELSITO: Yeah, I guess maybe that's a typo because I did say 15. Is that right, Priya, the max concentration is 15?

MS. CHERIAN: Yeah, the max concentration is 15.

DR. BELSITO: Okay. I just had a question about the grouping. So it says that, "No functions were reported for Galactonolactone, Glucarolactone, or Ribonolactone." I thought we needed similar functions to group. Is that not correct?

MS. FIUME: Typically, we don't use function for grouping because we're not always sure that the functions that are listed in the *Dictionary* are completely accurate or complete. Generally, it's based on the composition or the chemistry of the ingredients.

DR. BELSITO: Okay.

DR. ANSELL: But we do include when we're adding/using materials with no use, that the expectation is that they're used in the same concentration and application.

DR. BELSITO: Okay, that's fine.

DR. LIEBLER: And plus, chemically they go together. They're fine.

DR. ANSELL: Right.

DR. BELSITO: Okay. Then, go ahead.

MS. FIUME: I was going to say, what Jay just said, we don't consider that function; we consider that use information for the caveat in the conclusion.

DR. BELSITO: Okay. Then so for the Gluconolactones, since it's active ingredient in drugs we don't need other tox endpoints. That should go in the discussion. On PDF page 14 the carcinogenicity study, I really didn't follow this. So, Paul what did you think? Was the presumption that the findings were due to the meat and not the Gluconolactone? The nitrosamines in the meat?

DR. LIEBLER: Paul, you must be muted.

DR. SNYDER: Yeah, I had that down as questionable because I don't know how they came up with that interpretation.

DR. BELSITO: Okay.

MS. CHERIAN: Would it be helpful -- sorry.

DR. LIEBLER: I was just going to say it's as if the meat was a weird vehicle for the chemicals.

MS. CHERIAN: I was looking at the original study because the other group had brought this up too and would it be helpful if I just wrote it from a standpoint of rats fed the meat with Gluconolactone versus rats fed the meat without Gluconolactone instead of the nitrates?

DR. SNYDER: Yes. I'm assuming that there was no difference between the one percent gluconolactone, between the meat versus the control. That's the group I'm interested in: the one percent and the control.

MS. CHERIAN: Right, so I can rewrite it like that.

DR. SNYDER: Can you just delete the nitrosamine stuff out of there because that's not relevant to what we're --

DR. BELSITO: So you would delete that entire sentence, Paul, in addition to all treated groups in addition to nitrosamine carcinogenesis? Paul, you must be muted.

DR. SNYDER: Sorry, yeah, as long as the one percent is clean, it's no different compared to the controls then. You basically have the Gluconolactone control group for the nitrite plus Gluconolactone in sodium nitrate, so that's the only one that's relevant to us.

DR. BELSITO: Okay, so we're just going to delete that sentence?

MS. FIUME: First, does Priya need to check because it says all treated groups? So the one percent Gluconolactone is a treated group, right, so those results were probably seen there.

DR. SNYDER: I think she's got all groups treated with nitrosamine.

MS. CHERIAN: Right, because nitrosamine carcinogenesis would only show up with nitrate-treated groups.

DR. SNYDER: I mean, that's the way I read it. Let's just verify it and then write it that way because that's the only group that's relevant to us.

MS. CHERIAN: Right. I think the only thing that was noted was random tumors that were noted in both the control and the treated groups.

DR. BELSITO: So are we keeping that sentence or are we deleting it? I'm not following here.

DR. SNYDER: I would delete that tumor and say no tumors could be related to the administration of meat treated with gluconolactone.

DR. BELSITO: Okay, and just get rid of the sentence before it.

DR. SNYDER: Yeah.

DR. BELSITO: Okay. Done. So, in the discussion, we need the respiratory boilerplate. Anything for the discussion? The insufficiencies, obviously. And right now, we're going out with an IDA insufficient for manufacturing for Glucarolactone and Glucoheptenolactone, impurities in all except Gluconolactone, sensitization at 15 percent Gluconolactone, and that's all I have for data needs.

DR. LIEBLER: Yep. That's what I got.

DR. BELSITO: Paul, any additional?

DR. SNYDER: No.

Cohen Team – September 13, 2021

DR. COHEN: This is a draft report. It's the first time we're reviewing it. The safety assessment is on five derived ingredients. It's used as a skin conditioning agent. We have max use of 0.3 percent at rinse off and 15 percent in leave-on. We have frequency of use reported. We have method of manufacturing for three of the items. It's GRAS and used in foods for the glycolactone, and we have an HRIPT at 0.4 percent for glycolactone. I think we need irritation and sensitization at max use, and the other question is about the eyes again. Do we need an ocular tox? It's used around the eyes and in baby products. Comments, Lisa?

DR. PETERSON: We're missing method of manufacturing for the Glucarolactone, but there's no reported function or use. The glucoheptonolactone was missing manufacturing. There's no reported use, but there's a reported function. And that we didn't have impurities for any of them except for the gluconolactone.

I thought, since you're asking for more information, I would ask for those. I don't know how important it is to get them when there's no reported use, but I thought we should start by asking.

DR. SHANK: No reported use and no function. I think they could be removed from the report.

DR. PETERSON: Yeah, that was my other question, given the issues that were going to be discussed on some of these future things, if there was no function, no reported use, does it really belong in the report?

DR. COHEN: What's the common practice for us doing that?

DR. PETERSON: I mean, the funny thing is that, you know, and this is what I was going to get to when we got to that discussion is, in some reports we do have compounds listed that do have no reported uses. I mean, there's some inconsistency in what happens between different reports, and I just had a question about that.

DR. HELDRETH: So I think I can chime in on that. In the past, we kind of were pressuring to try to include as many ingredients as possible to cover -- the safety assessments that we do, to cover as many ingredients as possible. That really isn't a priority for us anymore going forward, and so, you will see for our priorities list for next year, the ingredients that are grouped together either must have some reported use or have some potential as a solid read across source for those ingredients that do have uses. Otherwise, we just won't include them in there.

If we were making this report for, off the 2022 priorities list, it probably would have only included one ingredient here. And that's what we'll see going forward.

Typically, in the past though, for reports where the writer has already constructed the report and put everything in there, we typically try to leave the ingredients in. But it is the Panel's prerogative, if you think that it's causing a problem or bogging the report down to have these other ingredients in the report, you can remove them.

DR. PETERSON: Well, I thought for the compound that's used you actually have a pretty good story, and so that, by including these other ones, it's holding things up because you would need to request for information because it's missing.

DR. SHANK: Right.

DR. COHEN: This is a draft report, so, if we went out and asked for that information and received nothing, our next go around we could move to remove them at that point, no?

DR. HELDRETH: Yes.

DR. COHEN: So, it's the early days. We might as well ask. So, Lisa, you wanted method of manufacturing for glucoheptonolactone and what else? And galacto?

DR. PETERSON: The second one. I'm terrible at pronouncing these.

DR. COHEN: Glucarolactone, right?

DR. PETERSON: Right, and then you want impurities on all of the ones that don't have impurities. Yeah, impurities on all of the ones that don't have impurities, which is everything except for the main, the one that's used.

DR. COHEN: Right. Tom?

DR. SLAGA: I agree, it's early in the process, so we should ask for data. Just a general that the -- can there be like a read across? I mean, all of these compounds are very similar, right?

DR. PETERSON: They are pretty similar, just one has a carboxylic acid. All the rest of them are stereo, you know --

DR. SLAGA: Right, and --

DR. PETERSON: -- basically look the same. They're polyol kind of --

DR. SLAGA: Glycolactone, and you said as a read across to the rest of them? I mean, (inaudible) based on impurities.

DR. PETERSON: The only one I'm a little worried about is the Glucarolactone because it has the carboxylic acid, which could change things. It'll change the toxicokinetics, and the metabolism might be different, but all the other ones I think you could read across.

DR. COHEN: So the Glucarolactone has the carboxylic acid, may change its reactivity.

DR. PETERSON: Yeah, there, yeah, I mean it's going to change its metabolism, it's going to -- I mean, the other ones could be metabolized to the carboxylic acid. We don't really know, but --

DR. COHEN: If we really don't get much data from that one --

DR. SLAGA: Yeah.

DR. COHEN: -- that one may come out next round. Okay.

DR. SLAGA: Let's wait for the next --

DR. BERGFELD: You might consider in the next round of changing the title.

DR. SLAGA: Yeah. It's misleading.

DR. PETERSON: What's misleading about the title?

DR. BERGFELD: You'll only be looking at the gluco.

DR. SLAGA: Yeah.

DR. COHEN: Right. Not the whole family of glycolactones.

DR. BERGFELD: Yeah. Unless you keep some in.

DR. PETERSON: Right, right, right. I got it. I understand now. I understand what you were saying. If you only have one chemical, the title should be the name of that chemical.

DR. COHEN: But Tom's question is, listen, if you could read across and we can include the family and we get enough data, why not do that? Right? It just creates one less report in the future should these come online.

DR. SHANK: That makes sense.

DR. SLAGA: Yeah, and really, there's no really concern for the other compounds in my eye.

DR. PETERSON: No.

DR. COHEN: All right, we'll ask for the information. Ron, do you agree we need irritation sense for max use?

DR. SHANK: For the Glucarolactone, yes.

DR. COHEN: Right, well, we don't have anything else on it.

DR. SHANK: It's a GRAS compound, so we don't need anything else.

DR. SLAGA: Right.

DR. COHEN: Okay.

DR. SHANK: I have one question on the carcinogenicity studies, page 14. It says there's nitrosamine carcinogenesis, and that's basically, I think they're saying because there is sodium nitrite added to the diet, there's nitrosamine carcinogenesis. I don't see how that could possibly involve gluconolactone because there's no nitrogen in that molecule, so you won't get any nitrosyl compound. So that whole paragraph on page 14, carcinogenesis studies needs to be expanded to explain it.

DR. SLAGA: Right, at least in a discussion. I agree.

DR. PETERSON: Yeah, I also agree.

DR. SHANK: Okay.

DR. COHEN: You wouldn't put it right in that paragraph that it's mentioned?

DR. SHANK: I think it should certainly be in that paragraph, if there's more information from the report.

DR. BERGFELD: Well, to clarify the discussion.

DR. SHANK: What do they mean? Pardon me?

DR. BERGFELD: To clarify the discussion, any points that could be questionable, we bring into the discussion.

DR. SLAGA: Yeah.

DR. PETERSON: I mean, I guess I understood why it was included, but it isn't really all about the cosmetic ingredient, you know, it's more about red meat and nitrites and maybe the other things that can be present in food, but I didn't -- I doubt it could be misleading, but I guess you (inaudible).

DR. SHANK: It is misleading.

DR. PETERSON: -- you have to include it? I almost thought it could be taken out because it doesn't help. It only leads to confusion.

DR. SLAGA: Right, it shouldn't be there. I agree.

DR. BERGFELD: So you're taking it out?

DR. COHEN: Can we take it out?

DR. PETERSON: Yeah, unless there's some reason for putting it in. Because of how it's done, the question isn't really about whether that -- the cosmetic ingredient is a carcinogenic. They're looking at the role of nitrites and --

DR. SLAGA: Right.

DR. PETERSON: -- meat, and I couldn't find the actual report, but, you know, I just think that this -- the chemical we're interested in is a bystander carried along for the ride somehow. And it's going to confuse anybody that reads it. They're going to all of a sudden get worried.

DR. SHANK: Correct.

DR. COHEN: So we're in agreement to remove it?

DR. SLAGA: Yes.

DR. SHANK: Yes, I agree with that.

MS. CHERIAN: Just to be clear, are we removing the sentence about nitrosamine carcinogenesis or the whole study?

DR. SHANK: Well, the study offers no information other than the fact that tumors were seen in the test animals.

MS. CHERIAN: Okay.

DR. SHANK: It has nothing to do with the cosmetic ingredient. It has to do with nitrite and meat, and that's an old story.

DR. SLAGA: Yeah.

DR. EISENMANN: So, if there was a group with just the material of interest, that group should be in, but the other information maybe should not be in? I wasn't a hundred percent clear if there was a group with just gluconolactone. That's what you should check. In one case it does make it sound like that, but in another part of it where you're discussing that study, it's not clear.

DR. SHANK: Are we talking about the same thing? The carcinogenicity studies?

DR. EISENMANN: Yes, yes. I thought maybe there was a group in there that they treated them just with meat containing the gluconolactone and not also nitrites, so in other words, there was a control with just the gluconolactone alone that had no cancer.

DR. PETERSON: I mean, the way it's written in the --

DR. SHANK: Well, it says all treated groups.

DR. SLAGA: Yeah.

DR. EISENMANN: So I wasn't clear if there was. So, if there is a group that's just the material of interest, that probably should be left in, but, if there is no group with just the material, then the study should come out.

DR. COHEN: They both had sodium nitrite in their diet, right?

DR. SLAGA: Right.

DR. COHEN: Is there a typo that the gluconolactone 0.5 sodium nitrite is just listed twice? Is there three groups, but the first two groups look like, separated by a comma, that they're the same thing. Right? You're talking about the Wistar rats, right? Were fed diets containing meat treated with either 1 percent gluconolactone, 0.5 percent sodium nitrite, 1 percent gluconolactone, and 0.5 percent sodium nitrite, isn't that redundant?

DR. PETERSON: No, I think it's just you're misreading. There was one group that just got the meat plus the lactone, then there's another group that got meat plus nitrite, then there was another group that got meat plus lactone plus nitrite at one concentration of nitrite, and another group that's got both. That's how I read it. That you had -- so what you want to do is see if there is a difference between meat plus and minus the lactone. If there were groups like that, but --

DR. COHEN: So, how many groups, Lisa?

DR. PETERSON: It sounds like there is a control group, if I'm reading this right, but I couldn't find the -- I wasn't able to pull the report up. It sounds like there was one control group got -- that was meat -- that was just meat by itself and that there was one group that got meat and the gluconolactone without the nitrite. That's how I read this.

That there was one, two, three, four, five groups. One just got meat, one got meat plus lactone, one got meat plus nitrite at the highest concentration, one got meat plus lactone and nitrite at one concentration, one got meat plus sodium nitrite at a lower concentration plus the lactone. That's how I read what was written.

And so theoretically, you could compare meat plus and minus the lactone, those two groups, and leave it in the report. That just says -- and then report the difference between the meat alone, plus the meat, plus the gluconolactone.

DR. COHEN: So you're suggesting that -- I see a group that had gluconolactone and 0.02 percent sodium nitrite. Did you see a group that just had gluconolactone without any nitrites?

DR. PETERSON: Yes, that's how I read that paragraph, that the first -- so it says with either one percent gluconolactone.

DR. COHEN: Ah.

DR. PETERSON: Then the next group would be meat plus five percent sodium nitrite.

DR. COHEN: I see, I see. Okay.

DR. PETERSON: The next group would be the --

DR. COHEN: Yeah, I get it.

DR. PETERSON: -- the lactone plus nitrite.

DR. SHANK: It should be that way, but it's still very confusing. If the study was properly designed, you would have the, what, five groups. So that paragraph needs to be expanded to make that clear, and then it says, "These tumors were seen in all of the treated groups." What is treated?

DR. COHEN: Yeah, what does treatment mean? It's to Carol's point where we should include this because there's --

DR. SHANK: It has to be made clear.

DR. PETERSON: I mean, there is a sentence that says, "No tumors could be related to the administration of meat treated with gluconolactone." The second to the last sentence.

DR. SHANK: Yes, I see that.

DR. SLAGA: Yeah.

DR. SHANK: I still think it's a confusing paragraph.

DR. PETERSON: Right, it could be rewritten. I'm actually not sure what the -- because they're not giving the --

DR. SLAGA: Nitrite.

DR. PETERSON: The gluconolactone by itself, it's always with meat, but the meat with it versus the meat alone did not cause tumors, so I guess that's valuable information.

DR. SLAGA: Yeah. It's safe anyway.

DR. PETERSON: Yeah.

DR. COHEN: Won't we come back to the way Priya wrote it originally, because ultimately, maybe we just refine the paragraph a little bit so it's easier to read.

DR. SLAGA: Right.

DR. PETERSON: I think if they just made that, and then the animals receiving the nitrite, that there was increased carcinogenesis. That's what's probably meant by the nitrosamine carcinogenesis. It's the groups that got the sodium nitrite. Again, we're not looking -- I couldn't see the real data, but my guess is that all the groups that had the sodium nitrite showed an increase in carcinogenesis. That's how I would change that sentence then if you want to leave it in.

DR. HELDRETH: If we look at PDF page 14, at the very top, the last paragraph of the chronic tox. That paragraph is related to chronic tox from the same study as what we're discussing right now. So, while it doesn't get to the nitrosamine effects, it does a better job of describing the groups and that there is a control. I don't know if that helps the Panel there.

DR. COHEN: Yeah, when you go back and look at it, it certainly makes sense, but it's just the use of the commas makes you have to really interrogate the sentence very specifically to understand that there are many groups.

DR. BERGFELD: I think summarize four groups, and then number them, one, two, three, four, five, I guess.

DR. PETERSON: Yeah, that's how I would rewrite it.

DR. HELDRETH: I can certainly do that.

DR. COHEN: Someone just said, so we have it as safe, but we're issuing an IDA because we don't have irritation and sensitization at max use even for gluconolactone, right, we still need that.

DR. SHANK: Correct.

DR. COHEN: Yeah, okay.

DR. SHANK: I was the one who said it's safe.

DR. COHEN: No, I heard that and I'm like, what a minute, I just wanted to clarify.

DR. SHANK: Yeah, sorry. What I was trying to say and didn't was there are no other data needs besides sensitization, because of the GRAS status.

DR. PETERSON: Right.

DR. SLAGA: Yeah.

DR. COHEN: Got it.

DR. BERGFELD: Then you were adding --

DR. SHANK: I apologize.

DR. BERGFELD: -- you were adding the four add-ons and requesting methods of manufacturing and impurities and read across for the first three, and then, whatever you can get on the last one, the ribonolactone, I guess.

DR. COHEN: Yes. Right. Okay, we'll move on to yeast.

Full Panel – September 14, 2021

DR. COHEN: So, this is a draft report. This is the first time we're reviewing Glycolactones. This is an assessment of five derived ingredients. It's used as a skin conditioning agent. We have reported max use of .3 percent in a rinse-off and 15 percent in a leave-on. And we have frequency of use reported.

Our team came out with an insufficient data announcement asking for method of manufacturing for Glucarolactone and Glucoheptonolactone; impurities for the four, we have it for Gluconolactone; irritation and sensitization for max use concentration for Gluconolactone, that's the only one we have use and concentration data for; and it is GRAS so we don't need anything else there.

We felt the package was a strong start for Gluconolactone, but in the effort to deliver sort of as broad a report as possible we're asking for the other data that I've listed.

DR. BERGFELD: And that's a motion.

DR. BELSITO: Well, David, for once we totally agree, second that.

DR. BERGFELD: Whoa.

DR. COHEN: Woo-hoo.

DR. BERGFELD: Very good. Any other discussion? Any edits that need to be brought forward.

DR. COHEN: I would say Don and I do agree on things with some frequency.

DR. BERGFELD: We'll see. Okay, I'm going to call for the vote. All those opposed? Abstaining? Unanimous agreement, thank you. We're going to move on then to the next ingredient, which is a biggie, Dr. Belsito, on Yeast.

MARCH 2022 MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – March 7, 2022

DR. BELSITO: Yeah. Any other comments on Glucosamine's? OK, let's see if we can get gluconolactones done here. I'm saying this. There is also a wave 3 on these. OK, so. We're looking at the fact, in September 2021, we issued an IDA for this group, and we asked for method of manufacturing data for Glucarolactone, Galactonolactone, and Glucoheptonolactone, impurities data for four of them, irritation and sensitization data at maximum concentration of use. We've got an HRIPT on 106 subjects, 15% Gluconolactone was received. It was non-irritating and non-sensitizing, and that is basically what we got. So based upon that where are we with this documents? I thought we could go with Gluconolactone as safe as used Ribonolactone needs impurities and all the others needed manufacturing impurities. Assuming we keep them, given the lack of function in cosmetics. Then there were those three that didn't have a function anyway, that that was my thought. After looking at this so I'll open it up to the team.

DR. SNYDER: I agree with the split conclusion.

DR. LIEBLER: Me too.

DR. PAUL SNYDER: Almost there in less than.

DR. LIEBLER: No, I agree with you.. I agree with Don and Paul completely with what Don just said and those are my comments on the report too.

DR. BELSITO: So. Do we review ingredients that are in the dictionary without any reported function?

MONICE FIUME (CIR): We do because I mean, that does happen occasionally. Usually not that often, but we don't always know the function.

DR. BELSITO: OK. I mean we can keep them in their report. They'll just be insufficient data. OK. Then then just to go through it Gluconolactone safe is used right? Ribonolactone needs impurities, and all the others need manufacturing impurities and would and we're keeping them in their report.

DR. LIEBLER: Right.

DR. SNYDER: So Don, on page 17, should we put an asterisk by those where there's where there's no reported function?

DR. BELSITO: OK, hold on, Paul. I was just doing something. That we could, I mean that would be nice.

DR. SNYDER: I think that would help link back to the into to our conclusion.

MONICE FIUME (CIR): So I'm going to do a Bart impersonation here where the functions are not always informative or correct when they're provided. So I know Bart usually hasn't issue with relying on function for determining safety. I mean, it's the panel's prerogative to have it marked if you want. But yeah, I just know that that is an issue that Bart often has concern over is the functions in what they're listed as.

DR. BELSITO: OK. I mean then we don't need to star them. It's not a big deal. We're still saying they're insufficient. They are insufficient for manufacturing and impurities.

MONICE FIUME (CIR): So it's the panel's prerogative, but I just know I've heard Bart on this many times.

DR. BELSITO: I'm OK either way, I just raised it because I thought one of the reasons for grouping was chemical similarity in a similar function, and since we don't have function, how can you say the function is similar, but I'm OK keeping them in and in two years, you know wiping out other cosmetic ingredients that safety is not supported by, you know, just so we can go through this dictionary.

JAY ANSELL (PCPC): You know, to that point though, but we have often included members of the family, that have no reported uses, with the provision that were it to be used, it would be used consistent with the application and concentrations included within the report. So.

DR. BELSITO: That's true. I gotcha.

DR. KLAASSEN: I thought I read in the minutes from the other. Come from the other committee that Bart had said that they were thinking about a change in that. That you know, if there weren't uses, maybe they we wouldn't include anymore. Does anybody know anything about that?

JAY ANSELL (PCPC): I don't know specifically what Bart was a referring to, but our position is that the inclusion within a family should not be driven on whether the material is used or not but that the data is reliable from each ingredient to support all of the other ingredients . And I see Don raised his hand.

DONALD BJERKE (P&G): Yeah, the science and Support Committee issued a recommendation not to review ingredients that have no reported uses as a potential gain and efficiency. And the response we got back was yes, we hear you. Thank you. But we're going to continue to do it, which is perfectly fine.

DR. KLAASSEN: OK, let's clarify.

DR. LIEBLER: Yeah.

MONICE FIUME (CIR): I think I'd like to take it one step further in conversations about this with Bart is that if in ingredient has no views. And doesn't have any data that can support itself or other ingredients in the report. Then, as the priority list is being built, the tendency would be not to include those in the grouping because it doesn't provide any information either safety wise or use wise. So that is one thought right now.

JAY ANSELL (PCPC): Right. And that would be our position as well is that for efficiencies that the parent compound. Be identified because of its use. And those other materials would only be included if they provide data which is reliable for assessing of the of the parent compound.

MONICE FIUME (CIR): But then I'd also like to ask Dan for input, being that you know you are involved in the groupings as the Subcommittee on the for the for the panel, what are your thoughts on it?

DR. LIEBLER: Well. We include ingredients if we're asked to include them basically that's the overriding. Yeah, that's the way. I mean, there's no committee anymore. It's just me and I know it.

MONICE FIUME (CIR): It's a committee of 1.

DR. LIEBLER: And I don't really even get asked about that unless we're looking at priorities generally. I think that right now my understanding is that we're asked to include anything that's reasonably related that's in the dictionary. And so, we err on the side of inclusion and we typically, I mean I, I quickly see at the priority stage whether there are uses or functions and we just include them, and that, of course, leaves us with a bunch of insufficients in many, in many cases. And then we waste a lot of

time going through the insufficient process. I guess, I mean, we can tolerate that it does cause spin our wheels with insufficiencies on the other hand, if we don't go through the insufficient process, we don't. I don't think we vacuum up the available data that we need it just it takes one or two or sometimes three iterations that we report to arrive at the fact that we just aren't getting data on a particular ingredient, then we have to say insufficient. So, if we want to err on the side of inclusion of the possible ingredients, gathering the relevant data on the broadest, you know, number of dictionaries listed ingredients that are in a family. I think we're kind of stuck with our current process.

DR. DONALD BELSITO: Yeah. And I mean, I think at some point we need to address the fact that by having these ingredients in the dictionary, even though they're not used, we put ourselves up to public comment that there are X number of thousands of things being used in cosmetics. And you know why I have not been looked at for safety. So you know, I mean. Yeah, there's an advantage to looking at materials that we can group into a group and then saying the data is not sufficient usually because we don't have manufacturing or impurities. Because otherwise we're reading across for a lot of the other tox endpoints so. I can see the benefit of including them just you know, for. For transparency and for the public awareness that you know, I mean. Keep hammering back that you have this dictionary is. You know, just a wish list and many of the things listed there aren't even being used.

DR. LIEBLER: Or made.

DR. BELSITO: Yeah. OK. Any. So, then we have the wave three comments, any that really were just all editorial and I think can be included in?

DR. LIEBLER: I have. Yeah. One that was, I just want to comment on the second point definition and structure about how gluconolactone is involved in the glucose 6 phosphate dehydrogenase deficiency, I thought.

DR. BELSITO: Uh huh.

DR. LIEBLER: That point in the report is PDF 18 under at the very top of the page, and it just says Gluconolactone is also involved in the metabolic disorder called G6 PD dehydrogenase deficiency pathway. I think at that point is not really relevant to our assessment and that that sentence could be just deleted from the report and that was what I recommended, and that then obviates the Council comment.

DR. BELSITO: Yeah. So that we're striking that out.

DR. LIEBLER: Yeah. And I struck it out on my copy of the report.

DR. BELSITO: I just did as well, and I guess that will pop up in my comment section that I deleted something and we can discuss it tomorrow to make sure the other team is happy with it.

DR. LIEBLER: Right.

DR. BELSITO: So the draft discussion on these, we need the inhalation boilerplate conclusion, I've already given you. Animation boilerplates. Yeah, but data is otherwise sufficient for econolacktone, but for cagonolacktone we need impurities and for the others we need manufacturing impurities.

DR. LIEBLER: Agree.

DR. BELSITO: Anything else to go on the discussion other than the inhalation boilerplate and our lack of manufacturing impurities on the materials were not clearing.

DR. LIEBLER: Nope.

DR. BELSITO: Paul, Curt.

DR. SNYDER: No, I think you summarized it perfectly. I had one comment. So, when he's mentioned that there was going to be maybe an effort to update the VCRP. Data how it's collected, or something wasn't that is it correct to Monice?

MONICE FIUME (CIR): Not how it's correct collected, how it's presented in the…

DR. SNYDER: That was presented. So I was wondering if in the end when we do put the table together, what if we had an asterisk by those that had no reported uses and that has had asterisk at the bottom said if they if they were to be used it would be within the context of the use table with regards to the types of uses and the other concentrations or something. Would that be useful or not because that just.

DR. BELSITO: Well, we have that now. Usually there's a table that follows the table with a concentration of use is in the number that lists the ones where there is no current use and say if they were to be used, the expectation is yaddayaddayadda.

DR. SNYDER: OK.

MONICE FIUME: It's actually split so if there's an insufficient conclusion and there's no reported use that has a different, it takes it further, but right if things are found. The whole family is determined safe. We do add that astrisk saying that it's assumed that they're being used at the same. The same manners as the other reported in the in the table.

DR. LIEBLER: And that's after the conclusion.

MONICE FIUME (CIR): That's in the conclusion, yes.

DR. LIEBLER: Right, it's supposed to be in that little table at the end. Yeah. So that's where I'd split.

DR. SNYDER: Well, the only reason I'm saying is that in this report, it's kind of different cause. On page 25 we have Table 3 which is only lists frequency and concentration use for only one of the ingredients. We looked at it and it doesn't have a table that says no uses.

MONICE FIUME (CIR): It's indicated on PDF page 18. The four ingredients that are not in use.

DR. SNYDER: Yeah, I understand the narrative it does, but usually we don't. We usually include an all the ingredients in the table, the VCRP table.

MONICE FIUME (CIR): Often not in the table. Well, if we have ingredients that have no use according to VCRP and the industry survey, sometimes will include those in a second table which is just the listing. It all depends on the number of uses and if it's easier to present it as a second table or just present it in text. If you would like to always see that in an additional table, we could do that, but it's not in the use table. It's a separate listing.

DR. LIEBLER: Monice don't we typically have a footnote to the frequency of use table that lists the ingredients that have no reported uses.

DR. BELSITO: We typically have a separate table.

MONICE FIUME (CIR): No, no reported means per category for the category that's in that table that the frequency in concentration of use table only include ingredients that have uses.

DR. LIEBLER: Right, but for ingredients that have no uses and therefore no use data. It seems inefficient to have a full table for those. I thought that we had a listing typically right after the frequency of use table. For the ones that do have uses. I thought it used to be like a footnote there. In this case it would be a footnote after Table 3.

MONICE FIUME (CIR): Not usually, if anything, table four would say these have no reported uses according to the VCRP and Council survey and we would list them there.

DR. LIEBLER: OK. Well, I mean we can do that, and I think that's kind of what Paul was getting at.

DR, SNYDER: Yeah, yeah. And I think in most cases we do. I have. My guess is that because only one ingredient was in use that they were just listed in the text of the report. But we can add that listing in as a table four.

DR. BELSITO: Yeah, I had added in it just you know it follows our usual pattern.

DR. LIEBLER: Is that what you are talking about Paul?

DR. SNYDER: Yeah, I mean it, it just struck me that there was just that we have this elaborate conclusion with insufficient data announcement, but then we don't have any, there's no data there in that table, so.

DR. BELSITO:OK.

DR. SNYDER: Yeah. Yeah. I just think it's just we just need to be consistent in how we do it.

DR. BELSITO: OK.

MONICE FIUME (CIR): So can I ask because we've done this several different ways and we've gotten comments back from the Council. So, we've included that table, which is the listing of those with no uses according to FDA and industry when it's been as little as one or two ingredients and will receive comments that say why do you have this in here? It's only one or two ingredients listed. So can I take it as you would like to see it pretty much all the time, just so it's clear.

DR. BELSITO: Yeah.

MONICE FIUME (CIR): OK.

DR. LIEBLER: Yep.

MONICE FIUME (CIR): Thanks.

DR. SNYDER: Yeah, I do. I'm very relying on the table, so make sure that the table matches the narrative. I usually kind of verify that when I'm reading a report, but again, it's something you can discuss if you're going to talk about the VCRP had also can talk a little bit about how to tabulate it for presentation of the panel, and maybe there can propose a couple different looks if there's some new way to do it, there might be more beneficial for us.

MONICE FIUME (CIR): OK, I will be working on that for June. So, I'll see what I can come up with to make it as efficient as possible for the panel members.

DR. BELSITO: Thank you. So, It's 12:02pm, anything more on the glyoclactones before we break for lunch? And come back with our discussion on what to do with yeast.

DR. LIEBLER: Nothing else for me.

DR. BELSITO: OK.

DR. SNYDER: Nothing for me.

DR. BELSITO: So we'll regroup at 1:00 o'clock.

Cohen Team – March 7, 2022

DR. COHEN: Alright, it'll be an interesting discussion tomorrow. OK, let's go to glycolactones. OK, so in glycolactones in September, we issued an IDA. Requesting method of manufacturing for Glucarolactone, Gluconoheptonolactone, amd Galactonolactone, and impurities on four of the ingredients; good edits in the third wave. And I'll, I'll open it up for discussion.

DR. SHANK: Well, I think the Gluconolactone is safe as used. We have enough information. If the chemists, well if Dr. Liebler, is comfortable with read across for their other ingredients, leave them in the report. If he's not, then I'd say, safe is used for Gluconlactone. Insufficient for the others. Or just leave the report limit the report Gluconolactone. Now the other Glucarolactone is a component of kombucha tea. Oh, that probably can be considered a food.

Dr. COHEN:
So I think. This far into the report, right? Our initial read on this was that they were going to stay in together and we were comfortable with read across. I mean, why would we be questioning read across now?

DR. SHANK: OK.

DR. COHEN: This far along, I know we don't have it. We're down a chemist, but.

DR. SHANK: I didn't recall that we had agreed for read across last time.

DR. SHANK: So that's that.

DR. COHEN: I can't swear to that either.

DR. SLAGA: Yeah. So they are all safe.

DR. BERGFELD: Maybe Bart can refresh.

DR. HELDRETH: So when we put these on the priority list as a group, the two chemists agreed that this was a solid grouping. However, determining if read across is appropriate really requires a little bit more data than they would have had at the time. They just had chemical structures on a cursory search of what's out there. But think the two chemists would want to compare the available tox data in addition to the related structures, to really say if it if there's a good structure, activity relationship or not. But I agree it would be good to let Dan weigh in on that.

DR. LIEBLER: So. If this is a draft tentative report and I'm presenting tomorrow, I ought to be expected to have a conclusion of some sort, and it's I mean, it's fine. I don't have any problems saying like, well, if Dan says we're OK with a read across, we're going to go out as safe as used. But I guess in the current situation, because we're down a chemist, we're going to we're going to borrow, you know it's like when we were kids on the street with there'd be 1 quarterback for both teams sometimes. Are we doing that here tomorrow?

DR. SHANK: Yes.

DR. HELDRETH: I mean, I think you know the other team doesn't have a Tom Slaga. So you know they don't have carcinogenic expert I mean so you know I think it's fair lately we loan them Tom sometimes.

DR. COHEN:
We do have Bart here.

DR. SLAGA: Yeah.

DR. COHEN: I'm kind of the kingpin of the whole thing. So well, Bart, to you. At least with your review of this, do you feel that read across this appropriate?

DR. HELDRETH: Or I'll preface it is I'm not one of the experts. I don't get a vote because of, not as independent at the panel.

DR. COHEN: Yes. Yeah, right. Arms length on that. But we're just general advice.

DR. HELDRETH: But yes, I mean I put this group together because I thought these what I would call kind of, sugar-like molecules all had very similar structures and I would be surprised if something really popped out very different.

DR. COHEN: OK, I have my marching orders on that and we will get corroboration from the Belsito team if they feel comfortable with it. And Wilma, you'll get me a little slack on the on the motion.

DR. BERGFELD: I'll back off, right? Allow for comments.

DR. SHANK: We may need the inhalation resource document reference because Gluconolactone is used in a product that could be incidentally inhaled.

DR. HELDRETH: We can definitely add that.

DR. COHEN: Good, good. Any other comments, any other points for the discussion?

DR. BERGFELD: Did we need a disclaimer or regarding the good manufacturing practice in there? Yeah, the boilerplate we use for that. Is that a need here? I wrote down it was. Not sure it is.

DR. COHEN: So its' GMPs are listed when it's discussed as GRAS.

DR. BERGFELD: OK.

DR. COHEN: It says according to US FDA, Gluconolactone is GRAS as a direct human food ingredient. With no limitations other than CGMPs. But maybe that's not addressing what you're talking about.

DR. BERGFELD: Why I put that there? I must have read it.

DR. COHEN: OK. Wow. Ron, you're right again, but you're always right. So ah, but you were right again round that we would come we would catch up in the back 9. Literally almost the back 9.

DR. SHANK: Right.

Full Panel – March 8, 2022

DR. COHEN: OK, so glycolactones - we reviewed this in September and the Panel issued an insufficient data announcement for the ingredient group, which was five ingredients. We have Max use of 0.3% in our rinse off in 15% - we have frequency of use reported - we asked for method of manufacturing for two of the derived ingredients, and impurities on four. We received irritation and sensitization data at Max concentration. We got third wave data edits that were very good. And this is GRAS and used in foods for Gluconolactone. So, our motion is safe is used. And this is a special request that we wanted Dan to weigh in on the read across to corroborate the conclusion that we came to.

DR. LIEBLER: Safe as used for everything.

DR. COHEN: Yes.

DR. BELSITO: We didn't. We didn't catch that.

DR. LIEBLER: Oh, we stuck with our insufficiency's.

DR. COHEN: OK.

DR. LIEBLER: Yeah.

DR. BELSITO: We had.

DR. LIEBLER: Right.

DR. BELSITO: Ribonolactone needs and impurities and the others need manufacturing and impurities.

DR. COHEN: OK. Then then I'll withdraw that.

DR. LIEBLER: So. OK.

DR. COHEN: It's part of the question that we came up with, so will withdraw the motion and will have an idea or an insufficient data for. Don, they will all but Gluconolactone.

DR. BELSITO: The Gluconolactone was safe as used - Ribonolactone still need impurities and the others? We need manufacturing and impurities.

DR. COHEN: I will continue that motion.

Dr. SHANK: Glucarolactone is in kombucha tea, so can that be considered a food?

DR. BELSITO: What's in where?

DR. SHANK: Glucarolactone - That's one of the ingredients.

DR. BELSITO: Right.

DR. BELSITO: Or we don't have manufacturing impurities.

DR COHEN: We don't. We can keep that as insufficient data till we get more. Ron?

DR. SHANK: OK.

DR. BERGFELD: Dan, any comment?

DR. LIEBLER: No, no further comment.

DR. BERGFELD: Paul?

DR. SNYDER: No, I'm fine.

DR. BERGFELD: Curt?

DR. KLAASSEN: It's OK.

DR. BERGFELD: OK. Alright, it's going to go out as insufficient. I'd call the question. Then all those opposed. Abstaining. It's approved and insufficient report. Alright. Moving on to earth or dirt. Dr Belsito.

Safety Assessment of Glycolactones as Used in Cosmetics

Status: Draft Final Report for Panel Review
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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.; 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 members involved in this assessment: Lisa A. Peterson, Ph.D. and Ronald C. Shank, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Senior Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
cGMP	current good manufacturing processes
CPSC	Consumer Product Safety Commission
Council	Personal Care Products Council
DART	developmental and reproductive toxicity
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
ECHA	European Chemicals Agency
EU	European Union
FDA	Food and Drug Administration
GD	gestation day
GRAS	generally recognized as safe
HRIPT	human repeat insult patch test
K_{ow}	n-octanol/water partition coefficient
NOAEL	no-observable-adverse-effect-level
NR	not reported
OECD	Organisation for Economic Cooperation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
SIDS	screening information dataset
SLS	sodium lauryl sulfate
TEWL	transepidermal water loss
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 5 glycolactone ingredients. Glucoheptonolactone and Gluconolactone are reported to function in cosmetics as skin-conditioning agents – miscellaneous, and Gluconolactone is also reported to function as a chelating agent. No functions are reported for the other 3 ingredients. The Panel considered the available data and concluded that Gluconolactone is safe in cosmetics in the present practices of use and concentration described in this safety assessment; however, the Panel concluded the available data are insufficient to make a determination of safety for Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This is a safety assessment of the following 5 glycolactones as used in cosmetics:

Galactonolactone
Glucarolactone
Glucoheptonolactone
Gluconolactone
Ribonolactone

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Glucoheptonolactone and Gluconolactone are reported to be used as a skin-conditioning agent – miscellaneous (Table 1).[1] In addition, Gluconolactone is reported to function as an antiacne agent and chelating agent. It should be noted that anti-acne agent is considered a drug function in the United States (US), and therefore, use as such does not fall under the purview of the Expert Panel for Cosmetic Ingredient Safety (Panel). No cosmetic functions were reported for Galactonolactone, Glucarolactone, or Ribonolactone.

These ingredients are being reviewed together as they are all oxidized monosaccharides that readily equilibrate, via hydrolysis, to the retrospective organic acids. For example, Gluconolactone is soluble in water and hydrolyzes into gluconic acid spontaneously.[2] In 2019, the Panel published a safety assessment reviewing gluconic acid and its salts (calcium gluconate, potassium gluconate, and sodium gluconate).[3] These ingredients were considered safe as used in in cosmetics in the present practices of use and concentration (as described in that safety assessment). The full reports on these ingredients can be accessed 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 was found on the European Chemicals Agency (ECHA) database[4] or was available from the Organisation for Economic Cooperation and Development (OECD) screening information dataset (SIDS) reports.[5] Information from these sources is cited throughout this assessment. Please note that the ECHA website and OECD SIDS documents provide summaries of information generated by industry, and when cited herein, it is those summary data that are incorporated into this safety assessment.

CHEMISTRY

Definition and Structure

All ingredients reviewed in this report are oxidized derivatives of glucose or other monosaccharides.[6] The definitions, CAS numbers, and structures of these ingredients are provided in Table 1.

These polyhydroxy acids are characterized by a tetrahydropyran/furan substituted by a ketone group. The glycolactones are, typically, weakly basic and exist in many living organisms, ranging from bacteria to humans. For instance, within humans, Gluconolactone (CAS No. 90-80-2; Figure 1) participates in a number of enzymatic reactions, starting with biosynthesis from β-D-glucose 6-phosphate (which is mediated by the enzyme glucose-6-phosphate 1-dehydrogenase).

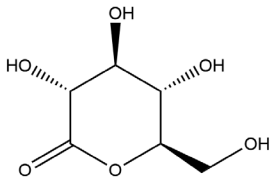


Figure 1. Gluconolactone

In addition, Gluconolactone can be converted into 6-phosphogluconic acid (which is mediated by the enzyme 6-phosphogluconolactonase).

Chemical Properties

The glycolactones reviewed in this report are water-soluble and have molecular weights that range from 148 g/mol to 208 g/mol.[6-9] The log K_{ow} for Gluconolactone is reported to be -2.2. Other chemical properties of the ingredients reviewed in this report are provided in Table 2.

Method of Manufacture

The methods below are general to the processing of glycolactones. No methods specific to cosmetic ingredient manufacture were found in the literature or submitted as unpublished data.

Galactonolactone

Galactonolactone can be prepared by the reduction of D-galacturonic acid by borohydride as follows. Via this method, D-galacturonic acid (10 g) is dissolved in 40 ml of water and neutralized with sodium hydroxide (pH between 8.5 and 9.0).[10] Next, borohydride is gradually added, constantly stirring, at room temperature. Samples are removed and acidified with acetic acid to remove excess borohydride, and boiled with a chemical reagent. After completion of the reduction, the solution is acidified with acetic acid, barium acetate is added, and the precipitate filtered off. Ethanol is added to the solution and the precipitate is collected. After the precipitate is washed with 60% ethanol, barium is removed with an ion exchange resin. One to 2 drops of n-butanol are then added to the precipitate, and the solution is concentrated to a syrup and dried. The lactone is recrystallized from absolute ethanol.

Gluconolactone

Gluconolactone may be prepared by direct crystallization from the aqueous solution of gluconic acid [21CFR184.1318]. Gluconic acid for food use in the US may be produced in any of three different ways: by the oxidation of D-glucose with bromide water, by the oxidization of D-glucose by microorganisms that are nonpathogenic and non-toxicogenic to man or other animals, and by the oxidation of D-glucose with enzymes derived from these organisms.

Ribonolactone

Ribonolactone may be prepared by oxidation of D-ribose with bromine in aqueous solution, followed by crystallization from ethanol.[11]

Impurities

Gluconolactone

According to the *Food Chemicals Codex*, food-grade Gluconolactone is sold as pure material, and is required to be no less than 99% and no more than 100.5% D-gluconolactone.[12] In addition, Gluconolactone should not contain more than 4 mg/kg lead, and may not contain more than 0.5% reducing substances (D-glucose).

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 and 2019 Council survey data, Gluconolactone is the only ingredient of this group that is reported to be used. According to the VCRP, this ingredient is reported to be used in 312 total formulations (195 leave-on and 117 rinse-off; Table 3).[13] The results of the concentration of use survey conducted by the Council indicate Gluconolactone is used at up to 15%, with the highest maximum concentration of use reported for other skin care preparations.[14] The 4 ingredients not in use, according to the VCRP and industry survey, are named in Table 4.

Cosmetic products containing Gluconolactone may be applied near the eyes, as it is reported to be used in eye lotions (concentration not reported), eye makeup removers (concentration not reported), and other eye makeup preparations (up to 0.075%). In addition, mucous membrane exposure may occur, as Gluconolactone is reported to be used in feminine wipes at concentrations up to 0.56%. Gluconolactone is also reported to be used in 3 baby product formulations (concentration of use not provided).

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.

The glycolactone ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[15]

Non-Cosmetic

According to the US FDA, Gluconolactone is a direct food substance affirmed as generally recognized as safe (GRAS), with no other limitations other that current good manufacturing practices (cGMP) [21CFR1318]. Gluconolactone is allowed for use in human food as a curing, pickling, leavening, and pH control agent [21CFR184.1318]. It is also used as a coagulant, acidulant [21CFR133.129, 21CFR155.120], and sequestrant in food processing.[16] In meat-packaging, Gluconolactone is used for color retention enhancement and as an emulsifying agent.[17] The use of Gluconolactone in meat products treated with nitrites provides a bacteriostatic effect. Gluconolactone is a natural constituent in several foods such as honey, fruit juices, wine, and many fermented products.[18] Glucarolactone can be found in kombucha teas.[19] Kombucha prepared from black tea contained approximately 5.23 g/l Glucarolactone.

In the US, Gluconolactone is an FDA-approved active ingredient that is used in conjunction with citric acid and magnesium carbonate to aid in the dissolution of bladder calculi.[20] Gluconolactone is also listed as an inactive ingredient in several intramuscular, intravenous, oral, and topical FDA-approved drug products.[21]

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion

Oral

Gluconolactone

Radioactivity was measured in the blood of normal and alloxan diabetic rats (strain not reported) after oral administration of [U-^{14}C] Gluconolactone (9 - 10 animals tested).[5] Animals were dosed with approximately 0.8 g/kg bw of the test substance via gavage. Radioactivity was also measured in the intestinal contents and feces 5 h after ingestion of the test materials. Intestinal absorption was rapid following oral administration of Gluconolactone. Initial oxidation occurred 4 h after administration of Gluconolactone and the oxidative turnover of Gluconolactone was significantly enhanced in diabetic animals.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

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

Chronic Toxicity Studies

Oral

Gluconolactone

Gluconolactone (99% purity) in water was given via gavage to Sprague-Dawley rats (10/sex/group) at doses of 250, 500, 1000, 2000, or 4000 mg/kg bw, for 6 mo.[4,5] Significant hematological changes were sporadic, not dose-dependent, and occurred in one sex only. Increased albumin levels and decreased cholesterol levels were noted in the 1000, 2000, and 4000 mg/kg bw groups. Significantly decreased blood urea nitrogen levels were also observed in males dosed with 4000 mg/kg bw Gluconolactone. No other dose-dependent clinical effects were noted. In all treated groups, thickening of the stratified squamous epithelium was detected in the anterior stomach, particularly the transitional area continuous with the pyloric stomach. Frequency and severity of this effect increased with dose. Submucosal inflammatory cell infiltration was detected in high dose groups; however, this effect was not observed in a statistically significant manner. No deaths or other abnormalities were detected.

Chronic oral toxicity of Gluconolactone was also evaluated in a 24-mo study involving Wistar rats (30/sex/group).[5] Animals were fed a diet containing 2.5% or 10% Gluconolactone (total intake of the test substance was 1240 - 1350 mg/kg bw in the 2.5% treated group, and 4920 - 5760 mg/kg bw in the 10% treated group). Weight gain was slightly reduced 2 - 3 mo after the initiation of administration of the test substance in the 10% Gluconolactone-treated group. Histopathological effects and number of deaths were similar among the control and treated groups.

In a 29-mo study, SPF-derived Wistar rats (30/sex/group) were fed diets of either untreated canned meat or canned meat treated with 1% Gluconolactone.[23] Blood samples for hematological investigations were taken from 10 animals in each group after 12, 24, 37, 51, 66, 78, and 91 wk. Bromosulphthalein determinations of serum glutamic-pyruvic transaminase activity were carried out at week 13 in 5 males/group and at week 26 in 5 females/group. Mortality rates, hematology,

clinical biochemistry, liver function tests, and histopathology revealed no differences between treated animals and controls. No other details regarding this study were provided. Results regarding carcinogenicity can be found in the Carcinogenicity section of this report.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Details regarding the DART studies summarized below are provided in Table 5.

Several developmental toxicity study summaries were available evaluating Gluconolactone.[5,24] The test substance was considered a non-teratogen in multiple species when administered orally (mice and rats at up to 4000 mg/kg bw (GD 6 - 15); hamsters at up to 560 mg/kg bw (GD 6 - 10); rabbits at up to 780 mg/kg bw (GD 6 - 18)).

GENOTOXICITY STUDIES

In Vitro

Gluconolactone

An Ames assay was performed on Gluconolactone according to OECD Test Guideline (TG) 471.[25] The test substance (Gluconolactone) was evaluated in *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 at concentrations of 2.5 and 5 µg/ml. Tests were performed with and without metabolic activation. No signs of genotoxicity were observed. Gluconolactone was also evaluated in a different Ames assay according to the same testing procedures as above on *Saccharomyces cerevisiae* strain D4. The test substance was tested at concentrations of 12.5 and 25 µg/ml, with and without metabolic activation. No genotoxicity was observed.

In Vivo

Gluconolactone

The potential genotoxicity of Gluconolactone was evaluated in a chromosomal aberration assay using male C57BL mice (2/group).[5] Mice were fed a single dose of either 2, 4, or 8 g/kg Gluconolactone, or a dose of 2 or 4 g/kg Gluconolactone, each day, for 4 d. Animals were killed after the last administration of the test substance. Approximately 0.3 ml of 500 µg/ml colchicine was intraperitoneally injected 1 h before mice were killed. At least 200 metaphase cells per mouse were examined. The test substance did not show mutagenic properties in the cells of mice administered single doses of Gluconolactone or in the cells of mice administered repeated doses of Gluconolactone.

CARCINOGENICITY STUDIES

Oral

Gluconolactone

In a 29-mo study, SPF-derived Wistar rats (30/sex/group) were fed diets of either untreated canned meat or canned meat treated with 1% Gluconolactone.[23] Throughout the experiment, the animals were inspected regularly for tumors. After 29 mo of treatment, the study was terminated and the remaining animals were killed and evaluated. Tumor incidence was similar in rats given treated meat versus untreated meat. No tumors could be related to the administration of meat treated with Gluconolactone.

OTHER RELEVANT STUDIES

Effect on Skin Barrier Function and Irritation

Gluconolactone

The effect of Gluconolactone on skin irritation prevention and skin barrier function was evaluated in 11 healthy subjects.[26] Gluconolactone (8%) in a base cream was applied to the skin of the subjects over an 8 cm x 5 cm test area, twice a day, for 4 wk. The base cream alone was applied to each subject to serve as a control. At week 4, a 5% sodium lauryl sulfate (SLS) challenge patch test was performed, under occlusion, for 6 h. Barrier function and skin irritation were evaluated by means of evaporimetry and chromametry weekly, and at 0, 24, and 48 h after SLS patch removal. After SLS challenge, Gluconolactone-treated sites resulted in significantly lower transepidermal water loss (TEWL) compared to the control sites. Similarly, erythema values were significantly reduced after irritation with SLS in Gluconolactone-treated sites compared to control sites.

DERMAL IRRITATION AND SENSITIZATION

Irritation

In Vitro

Gluconolactone

An in vitro skin irritation assay was performed according to OECD TG 439, using EpiSkin™ reconstituted human epidermis.[27] The test substance (a mixture containing 70 - 80% Gluconolactone) was considered to be non-irritating. No other details regarding this study were provided.

Sensitization

Human

Gluconolactone

A human repeated insult patch test (HRIPT) was performed on 105 subjects, using a test substance consisting of a white cream containing 0.041625% Gluconolactone.[28] The test article (0.1 - 0.15 g) was applied under an occlusive patch, to the back of each subject, 3 times a week, for 3 wk. After a 2-wk non-treatment period, a challenge patch was applied to a previously untreated site, and the site evaluated 24 and 72 h after application. The test substance was considered non-irritating and non-sensitizing.

HRIPTs were also performed, according to the same procedure as above ,using a product containing 1.4850% Gluconolactone (0.2 g; occlusive conditions; n = 100)[29] and a product containing 15% Gluconolactone (0.2 ml; occlusive conditions; n = 106).[30] No irritation or sensitization was noted in either study.

OCULAR IRRITATION STUDIES

In Vitro

Gluconolactone

An EpiOcular™ eye irritation assay was performed according to OECD TG 492.[27] The test substance (10% Gluconolactone) was not considered to be an irritant. No other details regarding this study were provided.

CLINICAL STUDIES

Clinical Trials with Gluconolactone-Containing Products

Gluconolactone

A 28-d, double-blind, within-person, study was performed in order to evaluate the effect of a product containing Gluconolactone in acne vulgaris patients (n = 25).[31] All subjects were asked to place the product (7% glycolic acid, 1% salicylic acid, 2% Gluconolactone, 0.05% licochalcone A, and adapalene (0.1%)) on each side of the face (0.25 g), once nightly, for 28 d. Patients were assessed on day 0, 7, 14, and 28. At each study visit, the safety profile, defined as the average score of erythema and scaling, was evaluated. Most patients reported an erythema and scaling score of ≤ 2 (no severe symptoms were reported). Results were similar at each evaluation period.

A double-blind clinical trial was performed on acne patients to evaluate the skin tolerance of an aqueous lotion containing 14% Gluconolactone (n = 50) in the treatment of mild to moderate acne when compared with its vehicle alone (base lotion; placebo; n = 50), or 5% benzoyl peroxide alone (n = 50).[32] Details regarding application were not provided. An initial baseline assessment was carried out, and patients were re-assessed at 2, 4, 8, and 12 wk. An assessment of skin tolerance was conducted at each review with respect to burning, stinging, erythema, scaling, pruritus, and dryness. There were no significant differences between the treatment groups for the clinical assessment of skin erythema, pruritis, burning, or stinging during treatment. Approximately 24% of the Gluconolactone-treated patients reported unwanted effects during the trial. Patients in the Gluconolactone-treated group reported more erythema, burning, stinging, pruritis, and scaling than those in the placebo group, however, these differences were not statistically significant.

SUMMARY

Of the 5 glycolactone ingredients reviewed in this report, Glucoheptonolactone and Gluconolactone are reported to function in cosmetics as skin-conditioning agents – miscellaneous. Gluconolactone is also reported to function in cosmetics as a chelating agent. No cosmetic functions were reported for the other 3 ingredients. These ingredients may readily equilibrate into their corresponding organic acids. For example, Gluconolactone is capable of spontaneously hydrolyzing into gluconic acid in aqueous solutions. In the US, food-grade Gluconolactone is sold as pure material, and is required to be no less than 99% and no more than 100.5% D-gluconolactone. Food grade Gluconolactone may not exceed 20 mg/kg in heavy metals or 10 mg/kg lead, and may not contain more than 0.5% reducing substances (D-glucose).

According to 2022 FDA VCRP data and 2019 Council survey results, Gluconolactone is reported to be used in 312 total formulations, with a maximum leave-on concentration of 15% in other skin care preparations. It is reported to be used near the eyes (up to 0.075%), in baby formulations (concentration of use not provided), and in formulations that may result in

mucous membrane exposure (up to 0.56% in feminine wipes). No cosmetic uses were reported for Galactonolactone, Glucarolactone, Glucoheptonolactone, or Ribonolactone.

According to the US FDA, Gluconolactone is GRAS as a direct human food ingredient, with no limitations, other than cGMP. In addition to being a curing, pickling, leavening, and pH control agent in various foods, Gluconolactone is a natural constituent is foods such as honey, fruit juices, wine, and many fermented products. Glucarolactone has been reported to be found in kombucha teas.

Radioactivity was measured in the blood of normal and alloxan diabetic rats after animals were given 0.8 g/kg bw of [U-^{14}C] Gluconolactone via gavage. Initial oxidation occurred 4 h after administration of Gluconolactone. The oxidative turnover of Gluconolactone was significantly enhanced in diabetic animals.

In a 6-mo study, Sprague-Dawley rats (10/sex/group) were given up to 4000 mg/kg bw Gluconolactone via gavage. No deaths, signs of clinical abnormalities, or dose-dependent hematological abnormalities were noted. Significantly decreased, dose-dependent, blood urea nitrogen levels were observed in males dosed with 4000 mg/kg bw Gluconolactone. Dose-dependent thickening of the stratified squamous epithelium was detected in the anterior stomach of treated animals. In a 24-mo study, Wistar rats (30/sex/group) were fed diets containing up to 5760 mg/kg bw Gluconolactone. Histopathological effects and number of deaths was similar among control and treated groups. Similarly, no differences were noted between control and treated groups in a 29-mo study involving SPF-derived Wistar rats (30/sex/group); rats were fed diets containing either untreated meat or meat treated with 1% Gluconolactone.

Several developmental toxicity study summaries were available evaluating Gluconolactone. The test substance was considered a non-teratogen in multiple species when administered orally (mice and rats at up to 4000 mg/kg bw (GD 6 - 15); hamsters at up to 560 mg/kg bw (GD 6 - 10); rabbits at up to 780 mg/kg bw (GD 6 - 18)).

Gluconolactone was not genotoxic in Ames assays involving *S. typhimurium* strains TA1535, TA1537, TA1538 (at concentrations of up to 5 µg/ml) and *Saccharomyces cerevisiae* strain D4 (at concentrations up to 25 µg/ml). Assays were performed with and without metabolic activation. An in vivo chromosomal aberration assay was performed in C57BL mice (2/group). Mice were fed a single dose of either 2, 4, or 8 g/kg Gluconolactone, or a dose of 2 or 4 g/kg Gluconolactone, each day, for 4 d. After observation of metaphase cells of the mice, no signs of mutagenicity were observed in any test group.

In a 29-mo study, SPF-derived Wistar rats (30/sex/group) were fed diets of either untreated canned meat or canned meat treated with 1% Gluconolactone. No tumors could be related to the administration of meat treated with Gluconolactone.

The effect of Gluconolactone on skin irritation prevention was evaluated in 11 healthy subjects. Gluconolactone (8%) in a base cream was applied to the skin of the subjects over an 8 cm x 5 cm test area, twice a day, for 4 wk. After 4 wk of administration, test sites were subjected to an SLS challenge patch test. Erythema values were significantly reduced after irritation with SLS in Gluconolactone-treated sites compared to control sites.

An in vitro skin irritation assay was performed according to OECD TG 439 using a test substance containing 70 - 80% Gluconolactone. The test substance was considered to be non-irritating. Gluconolactone did not produce irritation or sensitization in HRIPTs performed using various test substances (i.e., cream containing 0.041625% Gluconolactone, product containing 1.4850% Gluconolactone, and a product containing 15% Gluconolactone).

A test substance consisting of 10% Gluconolactone was not considered to be an ocular irritant in an EpiOcular™ in vitro eye irritation assay.

Acne vulgaris patients (n = 25) applied a product containing 2% Gluconolactone on each side of the face (0.25 g), once nightly, for 28 d. No severe symptoms were reported in any of the subjects after administration of the test substance. In a different study, the skin tolerance of an aqueous lotion containing 14% Gluconolactone was assessed in 150 patients (50 patients/group) with mild to moderate acne. A control group was treated with the vehicle (base lotion) alone and another group was treated with 5% benzoyl peroxide only. Applications occurred for 12 wk. There were no significant differences between the treatment and control groups for the clinical assessment of skin erythema, pruritis, burning, or stinging during treatment.

DISCUSSION

This assessment reviews the safety of 5 glycolactone ingredients as used in cosmetic formulations. The Panel reviewed the available data and concluded that Gluconolactone is safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that there is insufficient data to determine the safety of Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone.

The Panel determined that the use of Gluconolactone in food and drug products, as well as the available systemic toxicity data, were sufficient to mitigate any systemic toxicity concerns for this ingredient group. To make a determination of safety for the remaining ingredients (none of which are reported to be in use), the Panel requires impurities data for these ingredients, and cosmetic-specific method of manufacturing data for Glucarolactone and Glucoheptonolactone.

The Panel discussed the fact that Gluconolactone may be used in formulations that could potentially result in incidental inhalation (e.g., Gluconolactone is used in tonics, dressings, and other hair grooming aids at up to 0.6%). Toxicity data were not available; however, the oral toxicity data that were available did not report adverse effects. Additionally, 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 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, the concentrations at which the ingredients are used, and a lack of systemic toxicity, 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

The Expert Panel for Cosmetic Ingredient Safety concluded that Gluconolactone is safe in cosmetics in the present practices of use and concentration described in this safety assessment. Additionally, the Panel concluded the available data are insufficient to make a determination of safety for Galactonolactone,* Glucarolactone,* Glucoheptonolactone,* and Ribonolactone* under the intended conditions of use in cosmetic formulations.

* *There are currently no uses reported for these ingredients.*

TABLES

Table 1. INCI names, definitions, structures, and functions of the glycolactone ingredients in this safety assessment[1], CIR Staff

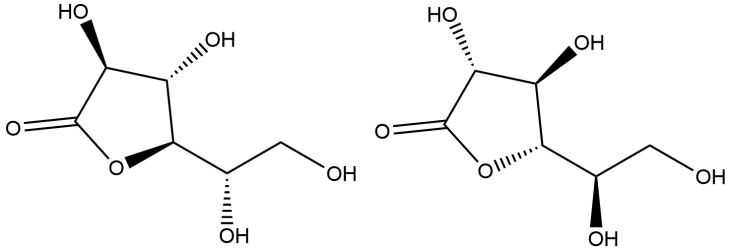
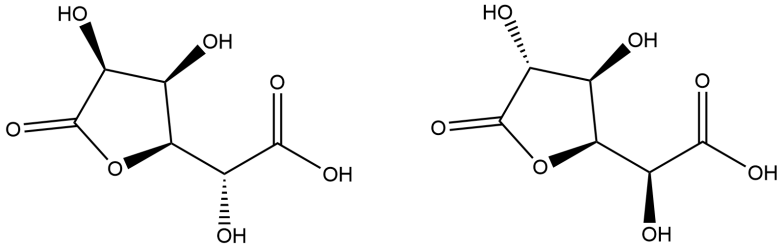
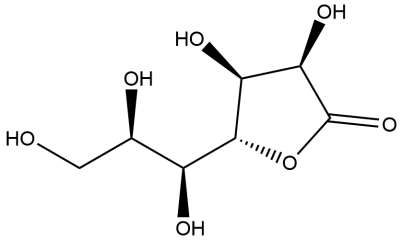
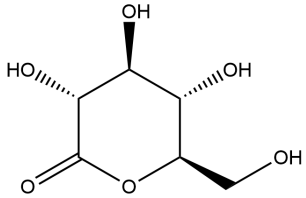
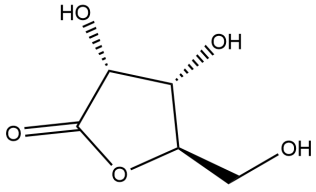
Ingredient	Definition	Function
Galactonolactone (CAS No. 1668-08-2 (L-) 2782-07-2 (D-))	Galactonolactone is the organic compound that conforms to the formula: 	Not Reported
Glucarolactone (CAS No. 2782-04-9; 389-36-6)	Glucarolactone is the organic compound that conforms to the formula: 	Not Reported
Glucoheptonolactone (CAS No. 60046-25-5)	Glucoheptonolactone is the organic compound that conforms to the formula: 	Skin-Conditioning Agents - Miscellaneous
Gluconolactone (CAS No. 90-80-2)	Gluconolactone is the lactone that conforms to the formula: 	Antiacne Agents; Chelating Agents; Skin-Conditioning Agents – Miscellaneous
Ribonolactone (CAS No. 5336-08-3)	Ribonolactone is the organic compound that conforms to the formula: 	Not Reported

Table 2. Chemical properties

Property	Value	Reference
Galactonolactone		
Physical Form	Solid, crystalline powder	7
Color	White	16
Odor	Odorless	16
Molecular Weight (g/mol)	178.14	7
Water Solubility (g/l)	583	7
log K_{ow}	-2.3	7
Glucarolactone		
Molecular Weight (g/mol)	192.12	9
log K_{ow}	-2.03 (estimated)	33
Glucoheptonolactone		
Molecular Weight (g/mol)	208.17	34
log K_{ow}	-3.02 (estimated)	33
Gluconolactone		
Physical Form	Solid	6
Color	White	5
Molecular Weight (g/mol)	178.14	6
Density/Specific Gravity (@ 20 ºC)	1.68	5
Melting Point (ºC)	153	5
Boiling Point (ºC)	398.5	5
Water Solubility (g/l)	586	6
log K_{ow}	-2.2	6
Disassociation constants (pKa)	3.70	5
Ribonolactone		
Physical Form	Solid	8
Molecular Weight (g/mol)	148.11	8
Water Solubility (g/l)	847	8
log K_{ow}	-2	8

Table 3. Frequency (2022) and concentration (2019) of use of Gluconolactone

	# of Uses[13]	Max Conc of Use (%)[14]
Totals*	**312**	**0.0000005 – 15**
Duration of Use		
Leave-On	*195*	*0.00001 – 15*
Rinse-Off	*117*	*0.0000005 – 0.3*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	13	0.075
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	59[a]; 93[b]	0.03 – 0.6[b]
Incidental Inhalation-Powder	59[a]; 2[c]	0.075 – 1.5[c]
Dermal Contact	223	0.0000005 – 15
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	89	0.03 – 0.6
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	14	0.56
Baby Products	3	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] 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
[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders

Table 4. Ingredients not reported to in use according to 2022 FDA VCRP and 2019 concentration of use data[13,14]

Galactonolactone
Glucarolactone
Glucoheptonolactone
Ribonolactone

Table 5. Oral developmental and reproductive toxicity studies on Gluconolactone

Animals/Group	Vehicle	Dose	Procedure	Results	Reference
CD-1 mouse (25 females/group)	Water	0, 6.95, 32.5, 150, 695 mg/kg bw	Animals were treated daily on days 6-15 of gestation; administration via gavage. Animals were observed daily for abnormalities. On day 17, all dams were subjected to caesarean section, and the number of implantation sites, resorption sites, and live and dead fetuses were recorded. External, visceral, and skeletal evaluations were performed on fetuses.	Parameters evaluated were similar among treated and control groups. Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 695 mg/kg bw	[24]
ICR mice (number of animals not reported)	Not reported	1000 and 4000 mg/kg bw	Animals were treated daily on days 6 to 15 of gestation; method of oral administration not stated	Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 4000 mg/kg bw	[5]
Wistar rat (25 females/group)	Water	0, 5.94, 27.6, 128, 594 mg/kg bw	Animals were treated daily on days 6-15 of gestation; administration via gavage. Animals were observed daily for abnormalities. On day 20, all animals were subjected to caesarean section, and the number of implantation sites, resorption sites, and live and dead fetuses were recorded. External, visceral, and skeletal evaluations were performed on fetuses.	Parameters evaluated were similar among treated and control groups. Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 594 mg/kg bw	[24]
Sprague-Dawley rat (number of animals not reported)	Not reported	1000 and 4000 mg/kg bw	Animals were treated daily on days 6-15 of gestation; method of oral administration not reported	Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 4000 mg/kg bw	[5]
Golden Hamster (22-27 females/ group)	Water	0, 5.6, 26, 121, 560 mg/kg bw	Animals were treated daily on days 6-10 of gestation; administration via gavage. Animals were observed daily for abnormalities. On day 14, all animals were subjected to caesarean section, and the number of implantation sites, resorption sites, and live and dead fetuses were recorded. External, visceral, and skeletal evaluations were performed on fetuses.	Parameters evaluated were similar among treated and control groups. Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 560 mg/kg bw	[24]
Dutch rabbit (14-17 animals/ group)	Water	0, 7.8, 36.2, 168.5, 780 mg/kg bw	Animals were treated daily on days 6-18 of gestation; administration via gavage. Animals were observed daily for abnormalities. On day 29, all animals were subjected to caesarean section, and the number of implantation sites, resorption sites, and live and dead fetuses were recorded. External, visceral, and skeletal evaluations were performed on fetuses.	Parameters evaluated were similar among treated and control groups. Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 780 mg/kg bw	[24]

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2022 FDA VCRP data – Glycolactones **Priya Cherian**

Gluconolactone

Baby Lotions, Oils, Powders, and Creams	2
Other Baby Products	1
Eye Lotion	7
Eye Makeup Remover	1
Other Eye Makeup Preparations	5
Hair Conditioner	30
Hair Straighteners	1
Rinses (non-coloring)	1
Shampoos (non-coloring)	38
Tonics, Dressings, and Other Hair Grooming Aids	13
Other Hair Preparations	6
Leg and Body Paints	1
Other Makeup Preparations	1
Bath Soaps and Detergents	5
Other Personal Cleanliness Products	9
Aftershave Lotion	1
Cleansing	28
Face and Neck (exc shave)	53
Body and Hand (exc shave)	6
Moisturizing	59
Night	11
Paste Masks (mud packs)	4
Skin Fresheners	7
Other Skin Care Preps	19
Indoor Tanning Preparations	3

Total: 312