Safety Assessment of Glycolactones as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	February 11, 2022
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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.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: Lisa, A. Peterson, 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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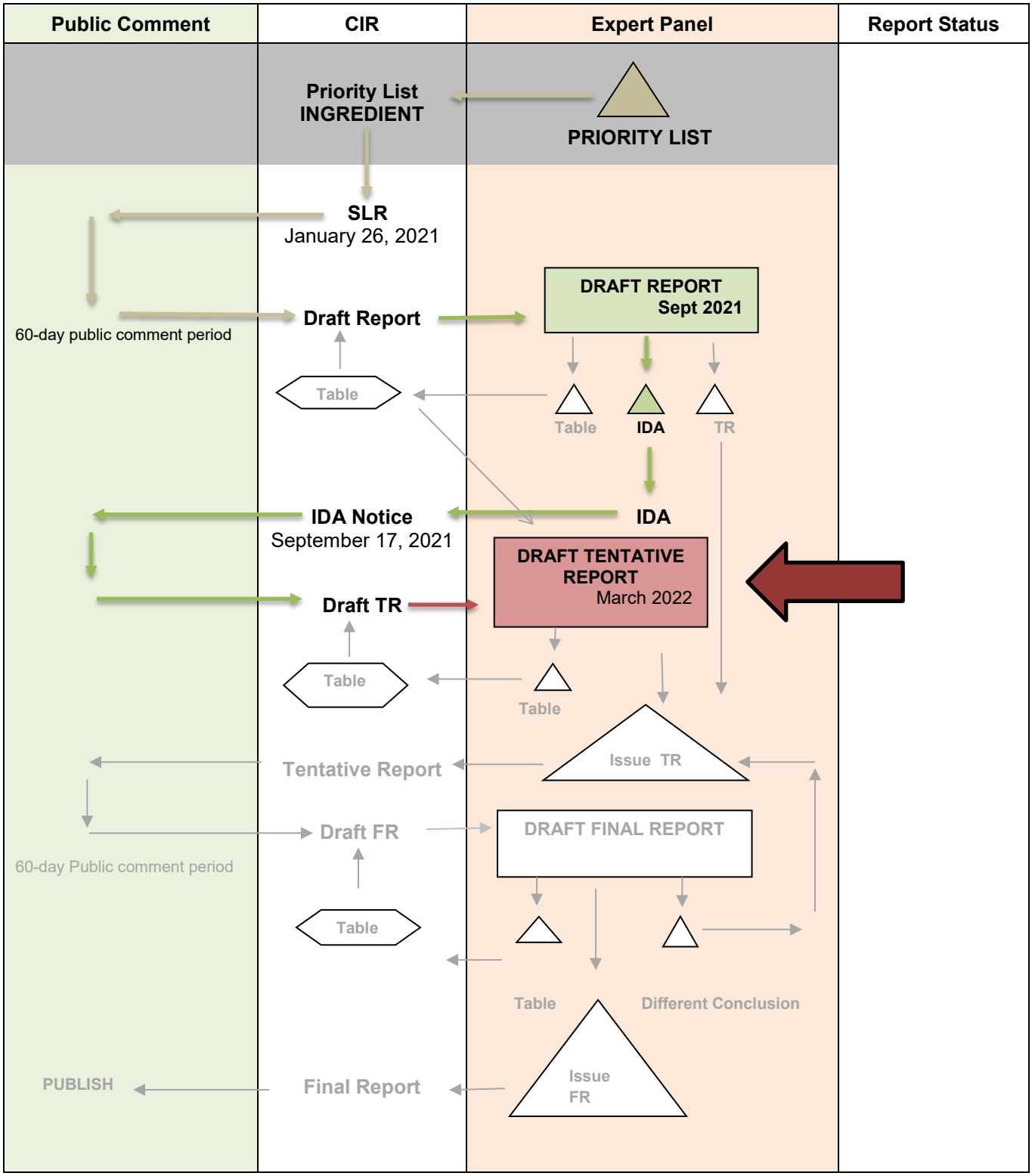
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Glycolactones

MEETING March 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: February 11, 2022
Subject: Safety Assessment of Glycolactones as Used in Cosmetics

Enclosed is the Draft Tentative Report of the Safety Assessment of Glycolactones as Used in Cosmetics (*report_Glycolactones_032022*). The ingredients reviewed in this report include Galactonolactone, Glucarolactone, Glucoheptonolactone, Gluconolactone, and Ribonolactone. At the September 2021 meeting, the Panel issued an Insufficient Data Announcement (IDA) for this ingredient group. In order to determine the safety of these ingredients, the Panel requested the following data:

- Method of manufacturing data for Glucarolactone and Glucoheptonolactone
- Impurities data on Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone
- Irritation and sensitization data at maximum concentrations of use

Since the issuing of the IDA, an HRIPT performed in 106 subjects using a product containing 15% Gluconolactone was received (*data1_Glycolactones_032022*). The test substance was considered to be non-irritating and non-sensitizing.

Included in this packet are the report history (*history_Glycolactones_032022*), data profile (*dataprofile_Glycolactones_032022*), search strategy (*search_Glycolactones_032022*), transcripts of the previous meeting (*transcripts_Glycolactones_032022*), and flow chart (*flow_Glycolactones_032022*). In addition, 2022 FDA VCRP data were received and incorporated into the report (*VCRP_Glycolactones_032022*). According to this data, Gluconolactone is still the only ingredient among this ingredient group that is reported to be in use. Compared to 2021 VCRP data, the number of uses for Gluconolactone has increased from 262 reported uses to 312 reported uses.

The Panel should carefully consider and discuss the data (or lack thereof), and the draft Abstract and draft Discussion presented in this report. A Tentative Report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion should then be issued.

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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

Glycolactones Data Profile – March 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 – March 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.

Safety Assessment of Glycolactones as Used in Cosmetics

Status:	Draft Tentative 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.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: Lisa, A. Peterson, 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
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

DRAFT 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 chelating agents. No functions were reported for the remaining ingredients. The Panel considered the available data and concluded that… [to be determined].

INTRODUCTION

This is a safety assessment of the following 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 be used as an antiacne agent and chelating agent. It should be noted that function as an anti-acne agent is not considered a cosmetic function in the United States (US), and therefore, use as such does not fall under the purview of the Panel. No 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.

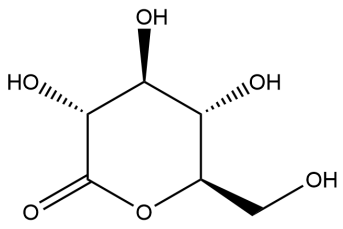
Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) database[4] or was available from the Organisation for Economic Cooperation and Development (OECD) screening information dataset (SIDS) reports.[5] Information from these sources is cited throughout 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. These 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).



In addition, Gluconolactone can be converted into 6-phosphogluconic acid (which is mediated by the enzyme 6-phosphogluconolactonase). Gluconolactone is also involved in the metabolic disorder called the glucose-6-phosphate dehydrogenase deficiency pathway.

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

According to 2022 VCRP and 2019 Council survey data, Gluconolactone is the only ingredient of this group that is reported to be used. In 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 ingredients not in use, according to the VCRP and industry survey include, Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone.

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).

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

Animal

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.

Human

Oral

Gluconolactone

Three male subjects were given either 5 g (84 mg/kg) or 10 g (167 mg/kg) Gluconolactone orally.[22] The amounts of Gluconolactone recovered in the urine 7 h after administration of 10 g Gluconolactone represented 7.7 - 15% of the administered dose. No pathological urine constituents were noted. When 5 g Gluconolactone were given orally, none of the administered dose was recovered in the urine. No other details regarding this study were provided.

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 effects 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 containing meat treated with either 1% Gluconolactone, 0.5% sodium nitrite, 1% Gluconolactone and 0.5% sodium nitrite, or 1% Gluconolactone and 0.02% sodium nitrite.[23] A control group was given meat without Gluconolactone or sodium nitrite treatment. 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 4.

Several reproductive 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

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

The glycolactones reviewed in this report are reported to function in cosmetics as skin-conditioning agents and chelating agents. 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 usually 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 human study, 3 males were given either 5 g or 10 g Gluconolactone, orally. The amounts of Gluconolactone recovered in the urine 7 h after administration of 10 g Gluconolactone represented 7.7 - 15% of the administered dose. No Gluconolactone was recovered in the urine after administration of 5 g Gluconolactone.

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, meat treated with 1% Gluconolactone, 0.5% sodium nitrite, 1% Gluconolactone and 0.5% sodium nitrite, or 1% Gluconolactone and 0.02% sodium nitrite.

Several reproductive 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 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 (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.

DRAFT DISCUSSION

[Note: This Discussion is in draft form, and changes will be made following the Panel meeting.]

This assessment reviews the safety of 5 glycolactone ingredients, as used in cosmetic formulations. The Panel concluded [TBD].

The Panel determined that the use of Gluconolactone in food and drug products, as well as the available systemic toxicity data, was sufficient to mitigate any systemic toxicity concerns for this ingredient group.

CONCLUSION

To be determined.

TABLES

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

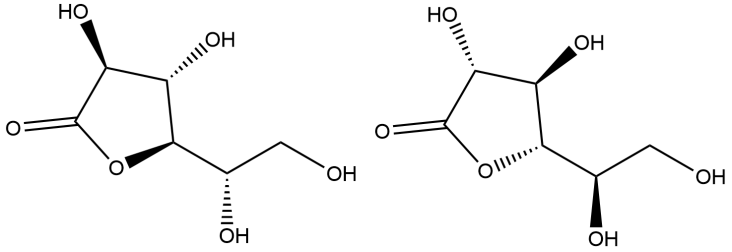
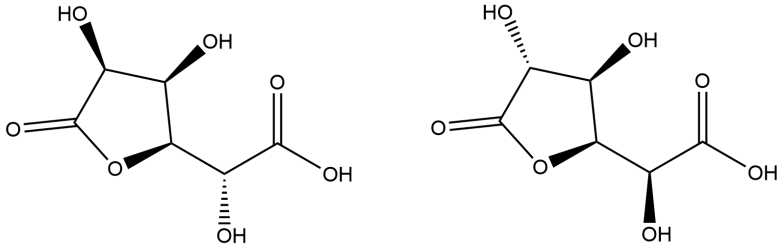
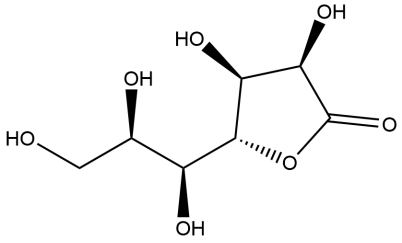
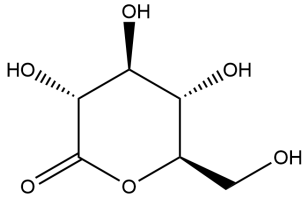
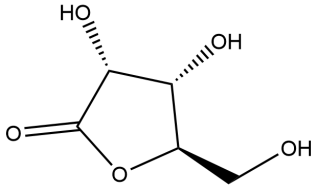
Ingredient	Definition	Function
Galactonolactone (CAS No. 1668-08-2 (L-) 2782-07-2 (D-))	Galactonolactone is the organic compound that conforms to the formula: 	Not Reported
Glucarolactone (CAS No. 2782-04-9; 389-36-6)	Glucarolactone is the organic compound that conforms to the formula: 	Not Reported
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. Oral developmental and reproductive toxicity studies

Test Article	Animals/Group	Vehicle	Dose	Procedure	Results	Reference
Gluconolactone	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]
Gluconolactone	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]
Gluconolactone	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]
Gluconolactone	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]
Gluconolactone	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]
Gluconolactone	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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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: September 22, 2021

SUBJECT: Gluconolactone

Consumer Product Testing Co. 2005. Repeated insult patch test (product containing 15% Gluconolactone)..

Consumer Product Testing Co.

EST. 1975

FINAL REPORT

CLIENT: [redacted]

ATTENTION: [redacted]

TEST: Repeated Insult Patch Test
Protocol No.: [redacted]

Product contains 15% Gluconolactone

TEST MATERIAL: [redacted]

EXPERIMENT REFERENCE NUMBER: [redacted]

[redacted]

[redacted]

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234

Consumer Product Testing Co.
EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: C05-0575.01

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of clinical laboratory studies. These studies have been performed with adherence to the applicable ICH Guideline E6 for Good Clinical Practice and requirements provided for in 21 CFR parts 50 and 56 and in accordance to standard operating procedures and applicable protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study. All data pertinent to this study will be stored in the Consumer Product Testing Company archive, unless specified otherwise, in writing by the Sponsor.

Quality Assurance personnel involved:

Quality Assurance — Date: 9.15.05

The representative signature of the Quality Assurance Unit signifies that this study has been performed in accordance with standard operating procedures and study protocol as well as government regulations regarding such procedures and protocols.

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234
Clinical • Toxicology • Analytical Chemistry • Microbiology

Objective: To determine by repetitive epidermal contact the potential of a test material to induce primary or cumulative irritation and/or allergic contact sensitization.

Participants: One hundred fourteen (114) qualified subjects, male and female, ranging in age from 16 to 77 years, were selected for this evaluation. One hundred six (106) subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Inclusion Criteria:

a. Male and female subjects, age 16[a] and over.
b. Absence of any visible skin disease which might be confused with a skin reaction from the test material.
c. Prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation.
d. Completion of a Medical History form and the understanding and signing of an Informed Consent form.
e. Considered reliable and capable of following directions.

Exclusion Criteria:

a. Ill health.
b. Under a doctor's care or taking medication(s) which could influence the outcome of the study.
c. Females who are pregnant or nursing.
d. A history of adverse reactions to cosmetics or other personal care products.

Test Material: [redacted]

Study Schedule:

Panel #	Initiation Date	Completion Date
20050329	July 13, 2005	August 25, 2005
20050336	July 18, 2005	August 25, 2005

[a]With parental or guardian consent

Methodology:

The upper back between the scapulae served as the treatment area. Approximately 0.2 ml of the test material, or an amount sufficient to cover the contact surface, was applied to the 3/4" x 3/4" absorbent pad portion of a clear adhesive dressing*. This was then applied to the appropriate treatment site to form an occlusive patch.

Induction Phase:

Patches were applied three (3) times per week (e.g., Monday, Wednesday, and Friday) for a total of nine (9) applications. The site was marked to ensure the continuity of patch application. Following supervised removal and scoring of the first Induction patch, participants were instructed to remove all subsequent Induction patches at home, twenty-four hours after application. The evaluation of this site was made again just prior to re-application. If a participant was unable to report for an assigned test day, one (1) makeup day was permitted. This day was added to the Induction period.

With the exception of the first supervised Induction Patch reading, if any test site exhibited a moderate (2-level) reaction during the Induction Phase, application was moved to an adjacent area. Applications are discontinued for the remainder of this test phase, if a moderate (2-level) reaction was observed on this new test site. Applications would also be discontinued if marked (3-level) or severe (4-level) reactivity was noted.

Rest periods consisted of twenty-four hours following each Tuesday and Thursday removal, and forty-eight hours following each Saturday removal.

Challenge Phase:

Approximately two (2) weeks after the final Induction patch application, a Challenge patch was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patch was removed and the site scored at the clinic twenty-four and seventy-two hours post-application.

*Manufactured by TruMed Technologies, Inc., Burnsville, MN

Evaluation Key:

0 = No visible skin reaction
+ = Barely perceptible or spotty erythema
1 = Mild erythema covering most of the test site
2 = Moderate erythema, possible presence of mild edema
3 = Marked erythema, possible edema
4 = Severe erythema, possible edema, vesiculation, bullae and/or ulceration

Results:

The results of each participant are appended (Table 1).

Observations remained within normal limits throughout the test interval.

Summary:

Under the conditions of this study, test material, [redacted] did not indicate a potential for dermal irritation or allergic contact sensitization.

Table 1

Panel #20050329

Individual Results

[redacted]

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	----------DID NOT COMPLETE STUDY----------									
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	----------DID NOT COMPLETE STUDY----------							
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch

Table 1
(continued)
Panel #20050329

Individual Results

[redacted]

Subject Number	Induction Phase 24*hr	1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
30	-	0	0	0	0	0	0	0	0	0	0	0
31	-	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0[m]	DID NOT COMPLETE STUDY			
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	----------DID NOT COMPLETE STUDY----------											
51	----------DID NOT COMPLETE STUDY----------											
52	----------DID NOT COMPLETE STUDY----------											
53	0	0	0	0	0	0	0	0	0	+	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
m = Additional makeup day granted at the discretion of the clinic supervisor
- = Subject not present for supervised removal
A = Changed to adjacent site

Table 1
(continued)
Panel # 20050336

Individual Results

[redacted]

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	----------DNC----------		
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
DNC = Did not complete study

Table 1
(continued)
Panel # 20050336

Individual Results

[redacted]

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	----------DID NOT COMPLETE STUDY----------							
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch

Table 2

Panel #20050329

Subject Data

Subject Number	Initials	Age	Sex
1	[redacted]	16	F
2		48	F
3		32	M
4		24	F
5		59	F
6		53	F
7		56	F
8		69	M
9		57	F
10		40	F
11		66	F
12		63	F
13		60	F
14		34	F
15		20	M
16		46	M
17		52	F
18		77	F
19		28	F
20		29	F
21		41	M
22		22	M
23		59	F
24		42	M
25		20	F
26		55	F
27		55	F
28		46	F
29		38	M

Table 2
(continued)
Panel #20050329

Subject Data

Subject Number	Initials	Age	Sex
30	[redacted]	49	F
31		20	F
32		32	M
33		30	F
34		39	M
35		74	M
36		25	F
37		70	M
38		55	F
39		74	M
40		52	F
41		63	F
42		65	M
43		58	F
44		54	F
45		61	M
46		57	F
47		43	F
48		70	F
49		74	F
50		74	F
51		22	F
52		69	M
53		37	M
54		67	F
55		66	M
56		36	F
57		55	F
58		47	F

Table 2
(continued)
Panel # 20050336

Subject Data

Subject Number	Initials	Age	Sex
1	[redacted]	47	F
2		66	F
3		49	M
4		51	F
5		75	F
6		71	F
7		27	F
8		66	F
9		69	M
10		68	F
11		68	F
12		62	F
13		70	F
14		75	F
15		28	F
16		67	F
17		44	F
18		47	M
19		20	F
20		76	F
21		65	F
22		16	F
23		18	M
24		75	F
25		77	M
26		53	F
27		45	M
28		28	M

Table 2
(continued)
Panel # 20050336

Subject Data

Subject Number	Initials	Age	Sex
29	[redacted]	41	F
30		55	M
31		70	F
32		32	M
33		53	F
34		32	F
35		40	F
36		36	F
37		53	F
38		34	M
39		74	F
40		24	F
41		42	F
42		59	F
43		60	F
44		57	F
45		18	F
46		53	F
47		41	F
48		35	F
49		63	F
50		27	F
51		61	F
52		41	F
53		40	F
54		48	M
55		17	F
56		56	F

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