Safety Assessment of Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate as Used in Cosmetics

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

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

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

Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

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

Date: February 16, 2021

Subject: Safety Assessment of Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate as Used in Cosmetics

Enclosed is the Draft Final Report on the Safety Assessment of Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate as Used in Cosmetics (identified as *tricit032021rep* in the pdf). This is the third time the Panel is seeing a safety assessment of these cosmetic ingredients. At the December 2020 Panel meeting, a Draft Tentative Report was presented to the Panel. Upon review, the Panel issued a Tentative Report, with the conclusion that these ingredients are safe as used in cosmetics in the present practices of use and concentration.

At the previous meeting, the Panel agreed to retain data for Hydroxy Tetramethylpiperidine Oxide as an additional cosmetic ingredient in this report. Corrected concentration of use data for Hydroxy Tetramethylpiperidine Oxide, received from Council in 2020, has been incorporated, reflecting a 0.019% maximum concentration of use in basecoats and undercoats, compared to the previously reported 12.9% (*tricit032021data*). Additionally, 2021 VCRP data have since been received and incorporated in the report (*tricit032021FDA*), showing an overall decrease in reported uses for Tris(Tetramethyl-hydroxypiperidinol) Citrate (from 388 to 125 formulations). Of note, reported uses in sprays have more than halved, and no baby product use has been reported in 2021. These and other changes are highlighted in yellow within the text.

Comments from Council on the Tentative Report were received and have been addressed (*tricit032021pcpc*). Included in this package for your review are a search strategy (*tricit032021strat*), report history (*tricit032021hist*), flowchart (*tricit032021flow*), transcripts from previous meetings (*tricit032021min*), and a data profile (*tricit032021prof*).

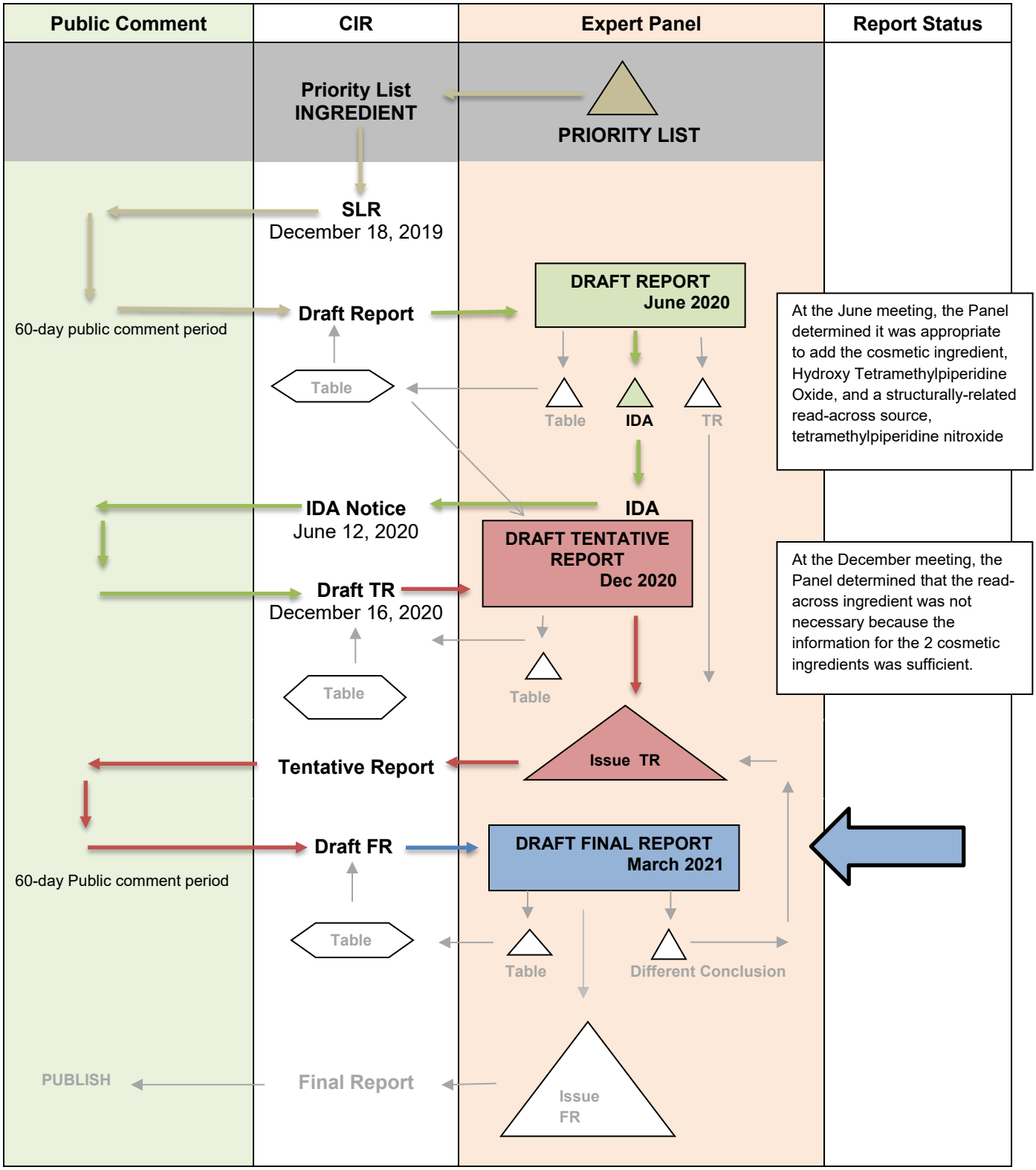
The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

1620 L Street, NW Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(email) cirinfo@cir-safety.org (website) www.cir-safety.org

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY _ Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate_

MEETING ___March 2021_____



CIR History of:

Tris(Tetramethylhydroxypiperidinol) Citrate

June 2018

-Concentration of use data submitted by Council

January 2020

-FDA frequency of use data obtained

December 2019

-Tris(Tetramethylhydroxypiperidinol) Citrate SLR posted on the CIR website

During the 60-day comment period, the following data was sought:

- Method of manufacturing, composition, impurities, UV absorption data (if absorbed, phototoxicity/photosensitization data may be needed), toxicokinetic data, (particularly dermal penetration data), and inhalation toxicity data

No unpublished data were received from Council or the industry.

March 2020

Council proposed the addition of data for 1 cosmetic ingredient (Hydroxy Tetramethylpiperidine Oxide, also known as Tempol; CAS No. 2226-96-2) and another structurally related non-cosmetic ingredient, tetramethylpiperidine nitroxide (also known as Tempo; CAS No. 2564-83-2).

June 2020

A Draft Report was presented to the Panel. An IDA was issued for method of manufacture and impurities.

The Panel approved the read-across addition of data from the two proposed ingredients.

- October 8, 2020: Concentration of use data were received from Council, for the added ingredient, Tempol

December 2020

A Draft Tentative Report was presented for Panel review. The Panel concluded that the non-cosmetic read-across ingredient, tetramethylpiperidine nitroxide, did not fill in any data gaps and was unnecessary. Lack of adverse effects in a 90-d dermal toxicity study for Tris Citrate, and the low likelihood of dermal penetration lead the Panel to issue a Tentative Report, with a safe as used conclusion for these ingredients.

The following were received after the December meeting:

- December 15, 2020: Updated concentration of use data for Hydroxy Tetramethylpiperidine Oxide
- January 21, 2020: 2021 VCRP data

January 2021

A Draft Final Report is being presented to the Panel for review

Tris(Tetramethylhydroxypiperidinol) Citrate Data Profile* – March 11-12, 2021 – Writer, Preethi Raj																															
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Hydroxy Tetramethylpiperidine Oxide	X			X			X	X			X			X	X	X				X			X				X			
Tris(Tetramethylhydroxypiperidinol) Citrate	X			X			X	X	X	X	X				X	X				X			X	X			X			

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

[Tris (Tetramethylhydroxypiperidinol) Citrate]

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Hydroxy Tetramethylpiperidine Oxide	2226-96-2	✓	0/0	NR	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tris (Tetramethylhydroxypiperidinol) Citrate	220410-74-2	✓	0/0	✓*	NR	NR	✓	NR	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR

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

Search Strategy

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

Note: The search term 'Tetramethylhydroxypiperidinol' was not searchable in PubMed

Tetramethylhydroxypiperidinol citrate cosmetics – 1/638
Tris citrate OR 220410-74-2 AND toxicity – 0/22
Tetramethylhydroxypiperidinol citrate OR 220410-72-2 AND toxicity – 0/3050
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND manufacturing – 0/186
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND chemical properties – 0/22,699
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND impurities – 0/91
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND toxicokinetics – 1/3205
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND dermal penetration – 1/3
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND dermal toxicity – 0/21
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND acute toxicity – 0/286
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND oral toxicity – 0/226
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND dermal sensitization – 0/6
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND dermal irritation -0/9
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND ocular irritation – 0/8
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND developmental toxicity – 0/56
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND reproductive toxicity – 0/138
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND genotoxicity – 0/72
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND carcinogenicity – 0/29
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND mutagenicity – 0/50
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND mucous membrane irritation – 0/2
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND epidemiology – 0/1,660
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND case report – 0/2,708
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND phototoxicity – 0/10

Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND UV absorber -0/0
Tetramethylhydroxypiperidinol citrate OR 220410-74-2 AND hypoallergenic – 0/0
Tinogard Q (tradename)– 0/0
tris(1,4-dihydroxy-2,2,6,6-tetramethylpiperidin-1-ium) 2-hydroxypropane-1,2,3-tricarboxylate (IUPAC name) – 0/0
General search:
tris(1,4-dihydroxy-2,2,6,6-tetramethylpiperidin-1-ium) 2-hydroxypropane-1,2,3-tricarboxylate – 2/1170
tris(1,4-dihydroxy-2,2,6,6-tetramethylpiperidin-1-ium) 2-hydroxypropane-1,2,3-tricarboxylate cosmetic toxicity – 0/30900

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

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/phytochem/search
- Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- European Medicines Agency Herbal Medicines - http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

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

JUNE 2020 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – June 8, 2020

DR. BELSITO: Okay. So this is Tris, Tetramethylhydroxypiperidinol citrate. And this is the first time we're looking at this. Used in 388 formulations including 335 leave-ons. So I guess the first question is the council thought whether it was appropriate to add data from a material we're not looking at, which is, I guess, Dan's idea at the end of the read-across that we talked about, 2,2,4,4-tetramethyl-4-piperidol-oxide. Which I presume is not a cosmetic ingredient. Is that correct, Bart?

DR. HELDRETH: Far as we know, yes.

DR. BELSITO: So, Dan, looking at that compound, would it be an appropriate read-across, do you think?

DR. LIEBLER: Where is that? I'm not seeing that.

DR. BELSITO: It came in the March 10th memo from Alex to Bart.

DR. LIEBLER: Oh, I'm sorry. I didn't note that. Let me -- what document would that be in, Bart?

DR. HELDRETH: March to June supplement.

MS. RAJ: Yeah. It's page 64 of the March to June supplement.

DR. LIEBLER: I thought I went through that, I'm sorry.

MS. RAJ: No worries.

DR. LIEBLER: And it's what page?

MS. RAJ: 64.

DR. LIEBLER: 64. You know what, it just says MI on the front of the supplement.

DR. SNYDER: No, that's not the right one. That's Wave 3. You have to go to the one that's June.

MS. RAJ: March to June.

DR. SNYDER: March to June. There were three waves. That comes at Wave 2.

MS. RAJ: Yeah. You're on it. Someone's sharing their screen. It's up now.

DR. LIEBLER: Yeah. That's good if you share the screen. I apologize. I'm sorry I got -- okay. Tox side. Yeah. Okay. I think that's fine.

MS. RAJ: So you think those are appropriate read-across?

DR. LIEBLER: I think so. It depends on the endpoint. Read-across always depends on the endpoint, so. March to June supplement. You know, I just may not have ever -- I might have gotten that document and didn't save it. And I don't have it in my list.

DR. BELSITO: We don't have the chemical structure of it, either.

DR. LIEBLER: No, I'm just trying to infer from the name. I think it's fine. It's four all oxide, which is the N-oxide. So it should be the N-oxide I think is what they're talking about. And that's very closely related. So I think that's an appropriate read-across.

MS. RAJ: Okay.

DR. LIEBLER: But it would depend on the endpoint.

DR. HELDRETH: We'll look through those dossiers and enter whatever data we find that's relevant into the next iteration of the document. Since this is only a draft report at this stage, you'll get to see it all laid out for you in there. Would you like us to try to use some of the same language for read-across that you gave to us in the glycerol ethoxylates?

DR. LIEBLER: Yes, please. Can I also ask a favor, Bart, or somebody? Email me this March to June. I just don't have that document.

DR. HELDRETH: Yeah. I can email it to you. It's also on the website.

DR. LIEBLER: I'll get it from the website. Don't worry about it.

DR. HELDRETH: It's in the right-hand column. It says March to June supplement.

DR. LIEBLER: Yeah. I don't know how I missed it. I apologize.

DR. BELSITO: It wasn't labeled a wave.

DR. LIEBLER: I only respond to waves.

DR. BELSITO: Okay. So, Daniel, you'll take a look at that, and then, if you feel differently tomorrow after looking at it, you can speak up.

DR. LIEBLER: Okay.

DR. BELSITO: So we don't have method of manufacture or impurities. I presume we need both.

DR. LIEBLER: Yes, we do.

DR. BELSITO: Okay. We don't have any absorption and distribution metabolism, but we do have a 90-day dermal. So will that help us for other tox endpoints?

DR. SNYDER: Yeah. We have an NOAEL -- a sub-chronic dermal that's 90 day. There was no NOAEL. It was at 150, and the maximum concentration of use of this is .05 percent. So I was not concerned about that.

DR. BELSITO: Okay. So that 90-day dermal clears us for endpoints other than skin. But we don't have DART. Does it clear us for DART?

DR. SNYDER: Yeah. I think so, too. I mean, the same thing with carcinogenicity. This NOAEL is very high in relationship to the maximum concentration of use of .05 percent. There were no genotox alerts, so I wasn't concerned about the carcinogenicity. Nor was I concerned about the reproductive.

DR. BELSITO: Okay. So that would be something, Preethi, that would need to go in the discussion.

MS. RAJ: Okay.

DR. BELSITO: Why we weren't concerned about lack of data on those endpoints because we have the 90-day dermal tox at a very high dose. And concentration of this material is .05.

MS. RAJ: Okay.

DR. BELSITO: So I thought it was -- first of all, it's used as a photostabilizer, which means it must absorb light. So I thought it was insufficient for UV spectrum, and it probably will absorb and, therefore, would be insufficient for photo irritation and photosensitization and insufficient for method of manufacture and impurities. Otherwise, I had personally no insufficiencies -- other insufficiencies, at least. Dan, Curt, Paul?

DR. LIEBLER: Yeah. Actually, this is interesting, Don, because the structures of the two components would not absorb light in the UV-vis. There's no chromophore in either the Tris Tetramethylhydroxypiperidinol part or the citrate. So if it's used as a light stabilizer, it may be that it's intended to react with excited molecules that do absorb light somehow.

But this should not absorb light. It shouldn't itself be likely to undergo photo-activation by the mechanisms that we typically associate with, you know, light absorbing, UV-vis absorbing photosensitizers. So I mean, I don't object to asking for that. But the rationale is not the same as for other things that do have chromophores.

DR. BELSITO: Okay. So since we're going insufficient for method of manufacture and impurities, we'll ask for UV spec. And then if we don't get it, we can use your argument that there's no chromophore and it's probably there to absorb reactive species.

DR. LIEBLER: Yeah. It'll be blank.

DR. BELSITO: Any other data needs for this? Curt, Paul?

DR. SNYDER: I have none.

DR. KLAASEN: No.

DR. BELSITO: Okay. And so then in the discussion, Preethi, we start talking about the 90-day dermal helping us with the lack of genotox or --

MS. RAJ: DART and carcinogenicity.

DR. BELSITO: Carcinogenicity, right.

MS. RAJ: And I guess at this point I don't need to add the language about the photostabilizer thing until we see first if we get some data on that, right?

DR. KLAASEN: Correct.

DR. BELSITO: I mean, just we're asking for the data. I mean, normally, we don't -- do you say why we're asking for it? I don't think so. We just say --

DR. HELDRETH: Right. At this point, this would go out as an insufficient data announcement for these data needs. And really it's great to have some advance notice of what should be in the discussion section, but it's not something we really have to worry about quite yet because we're not putting out a conclusion.

MS. RAJ: Okay. Thank you.

DR. BELSITO: Okay.

DR. SNYDER: Dan, would any of that information be in the citric acid report?

DR. LIEBLER: Citric acid is not going to absorb. You know, photo is not an issue. So I don't know. I don't think there would be anything in citric acid -- the report having anything to do with photo.

DR. SNYDER: Okay. Thank you.

DR. ANSELL: We have for the add-on a note that it's used as a free radical scavenger.

DR. LIEBLER: That's it. Yeah. And Tempo is the other molecule proposed to add as a read-across. It is a radical trap. It's used experimentally a lot. At least, it used to be.

DR. KLAASEN: Now, Dan, this Tris citrate, that's what we use in the lab all the time as a buffer?

DR. LIEBLER: The Tris part.

DR. KLAASEN: Okay. That's what I thought.

DR. LIEBLER: And you have Tris hydrochlorate acetate, et cetera, and various --

DR. KLAASEN: And we got quaternary nitrogen, so we're not going to have much absorption.

DR. LIEBLER: Nope. No chromophores there.

MS. RAJ: You all may have touched on this already, but I just wanted to ask is the panel, I guess, interested in getting data for the reactive cation part of this molecule? Or is it not of concern?

DR. LIEBLER: It's a cation part of the salt. It's equally relevant to the citrate. I would not use the term reactive to describe this cation. It's shouldn't cut out high chemical reactivity.

MS. RAJ: Okay.

DR. LIEBLER: I mean, it's fairly inert couple of molecules. The one difference between these, I suppose, is maybe the Tris part could actually penetrate skin. But we're already going to address the dermal tox. So citrate probably can't penetrate skin significantly.

MS. RAJ: Thank you.

DR. BELSITO: Anything else you need, Preethi?

MS. RAJ: So far, I guess not. We're just getting started, I guess, right? Will have to put an IDA out.

DR. BELSITO: Right. Any other comments, panel? Okay. So we're done with this one.

Marks Team – June 8, 2020

DR. MARKS: So this is the first review of this single ingredient, Tris Citrate, and Preethi has spelled out the long name for Tris. I'm going to continue referring to it as Tris rather than Tetramethylhydroxypiperidinol. Wow, that's a mouthful. Any rate, we don't have to worry about any add ons unless, Lisa, you and Dan got together in the back room and suggested any add ons. Okay. Good. None.

DR. PETERSON: No add ons to this one.

DR. MARKS: I see that nonverbal communication. Lisa, Ron, Tom, your comments? Do we have needs like method of manufacture, impurities, phototox data?

DR. PETERSON: Yes. Yep, we need method of manufacture and impurities for sure.

DR. MARKS: Phototox data since this is a light stabilizer? I'd hate for it to be a light sensitizer. So I added that also. Other needs? So it's going to be issue an insufficient data announcement. That sounds pretty straight forward. Any other comments, needs, Lisa, Ron, Tom?

DR. EISENMANN: I have a question for Lisa. The component, which is also called Tempol -- you know, the structure that's attached to the citrate -- is data on that relevant?

DR. PETERSON: Yeah. I would think so because the citrate is just a salt.

DR. EISENMANN: Because there's an ECHA dossier on that material. I don't remember exactly what studies are there, but that is -- I found the CAS number for it and have it in comments. It's a spin trap. It's called another -- the trade name for it is Tempol, T-E-M-P-O-L.

DR. PETERSON: Yeah, yeah, yeah. We use it for trapping radicals in biological circumstances or in chemical circumstances.

DR. MARKS: Carol, are you referring to Alex's comments on her 3/10 memo where she asked if adding data on 2,2,4,4-tetramethyl-4-p–oxide and the compound with the hydroxyl group are appropriate? That's what you're referring to, Carol?

DR. EISENMANN: Correct.

DR. MARKS: Yep. Okay. And, Lisa, that's what you're saying yes to.

DR. PETERSON: Well, let me make sure I'm yes to the right thing, but the chemical structure's the same, yes.

DR. EISENMANN: And then there's one without the hydroxyl group, which I wasn't sure about. But if there's enough data on the Tempol, you probably don't need any data on the other one.

DR. PETERSON: Right.

DR. EISENMANN: So there's --

DR. PETERSON: I mean, I think if you're looking for, I guess -- it has to be, I think, the same structure.

DR. EISENMANN: Okay.

DR. PETERSON: Because the hydroxyl group changes things a bit. And then the salt -- it's a salt with citrate.

DR. MARKS: Okay.

DR. PETERSON: In fact, the chemical functions are the same.

DR. MARKS: We've got a lot of other data there, endpoints, so is that all we need then? Tom and Ron, you're happy with the data you have on, you know, acute toxicity repeat? The DART? We don't have anything on DART that I can see. Genotox we have. Nothing on carcinogenicity. Is there anything on those that we need? Inhalation, we don't have.

DR. SHANK: Yes, we do have inhalation.

DR. MARKS: Oh, okay.

DR. SHANK: And genotox.

DR. MARKS: Yes.

DR. SHANK: And they don't indicate any significant toxicity potential. This seems to be slowly absorbed if at all. It has a Kow of minus 0.29 which supports little penetration, so I don't think DART is necessary. If the Panel feels that rationale is not valid, then you could ask for skin penetration data before you ask for DART. But I don't think the systemic toxicity is an issue. Impurities is. N-nitrosopiperidine is a carcinogen. I don't know if that's an impurity, but it may be.

MS. RAJ: But what might be an impurity, Dr. Shank?

DR. SHANK: N-nitrosopiperidine.

MS. RAJ: Okay.

DR. MARKS: Okay. Tom, did you have any other comments?

DR. SLAGA: No, I didn't see any toxicity data (inaudible).

DR. MARKS: I got the no. It's hard to hear you after that. If you want to type out anything, Monice will look at it in the chat, and we can address it. So tomorrow, I'll be seconding presumably a motion from the Belsito team to issue an insufficient data announcement. And the data needs we would like to see is method of manufacture, impurities, and phototox data. Sound good, Tom, Lisa, Ron?

DR. SHANK: I think phototox you said.

DR. MARKS: Yeah. I think if it's a light stabilizer, to me, that indicates it must somehow absorb the light or do something, and I just -- when you use that sort of function, I'm wondering what happens when light hits this compound. Could it become a sensitizer? It's certainly not a routine sensitizer, meaning without light, but is it a photo sensitizer? Ron, you're not worried about phototox with it?

DR. SHANK: Well, I just -- looking at the structure, it doesn't --

DR. PETERSON: Well, these things are used as radical traps, so it probably quenches the radicals that would be formed that would cause the degradation of the other materials present in the mixture.

DR. SHANK: Oh.

DR. PETERSON: So, I mean, it's used as a radical trap.

DR. MARKS: Okay. So you don't think, Lisa, that it -- for me --

DR. PETERSON: I have no idea.

DR. MARKS: -- my question was is it a light stabilizer because it's absorbing light? Ron, you think the structure would indicate it isn't going to absorb light. And Lisa, you think the mechanism is as a light stabilizer really that's a -- it's working because it's absorbing radicals.

DR. PETERSON: Yeah. The light would hit stuff in the mixture, and it could create radicals that could cause decomposition. And it basically quenches the radicals by holding them. And it's a relatively -- it's used in radical trapping things so that you can detect that radicals are present so that the radical that's formed is actually fairly stable.

DR. MARKS: Okay.

DR. PETERSON: Fairly stable.

DR. MARKS: Mm-hmm.

DR. PETERSON: But I don't know if there's any studies. It would be interesting to see if there were any studies about radicals and the concerns you have.

DR. MARKS: I'll tell you what, Ron Shank, can we put it on our wish list, and, if we don't get anything, then we'll just say we'll drop it the next time based on that reasoning? But, if you want me to drop it now, that's fine, too.

DR. SHANK: No, you can put it to your wish list.

DR. MARKS: Yeah. I think asking for a little more rather than a little less is -- in this case.

DR. SHANK: Right.

DR. MARKS: To me, that's just a red flag. And if we end up getting nothing -- I think in the discussion we need to indicate why, as a light stabilizer, we don't need phototox and use the reasoning as you suggest, Ron, that the structure would suggest that it's not absorbing light; and, Lisa, that it's mechanism of action for light stabilizing is it's stabilizing -- scooping up the radicals that are infused by light.

DR. PETERSON: Yeah. I think -- I'm sure it would be nice to know that there was a reference in the literature. I'm just -- I'm just hypothesizing.

DR. MARKS: Exactly. Yeah. No. No, I think if we are going to address it in the discussion, we should have that. Okay. Any other comments?

So tomorrow I'm going to, I think, assuredly second an IDA, an insufficient data announcement. And we have two to three: certainly, method of manufacture, impurities. And we'll see what Don perhaps has to say about the phototox. Okay. Any other comments?

MS. RAJ: It sounds like from the proposed read across from Council, only the Tempol maybe is of interest, not so much the one without the hydroxy or hydroxyl group.

DR. MARKS: I'll let you answer that, Lisa.

DR. PETERSON: Yeah. I mean, I'd have to think. I mean, you're asking me -- I didn't see that request, and so I'd have to think about it. But, you know, I think that the hydroxyl group -- I'd have to review, but I sort of think that it's -- yeah. I'd have to think about it a little bit.

DR. MARKS: Okay.

DR. PETERSON: I'd have to find out what the role of the hydroxyl group plays actually.

MS. RAJ: Okay.

DR. PETERSON: Can I get back to you on my opinion after I do a little checking?

MS. RAJ: Yeah. Absolutely. Absolutely.

DR. MARKS: Well, and then, Preethi, go ahead and ask that again tomorrow with Dan Liebler.

MS. RAJ: Okay.

DR. MARKS: And see what his comments are also. Yeah. That was the reason, Lisa, you may not have seen that. It was in Alex's 3/10 memo from industry, and she was asking whether I ought to -- and we got -- that was that one -- that March through whatever it was where there was a whole -- every ingredient she had comments about, and it was in that memo.

DR. PETERSON: Oh, it's the one that says March to June?

DR. MARKS: Yes.

DR. PETERSON: Okay. I'll take a look at it again more carefully.

DR. MARKS: Yeah. Okay.

DR. PETERSON: I'll maybe email you something, Preethi, and --

MS. RAJ: Okay. Sounds good.

DR. MARKS: Okay. Now, we get into pigmentation again. That's been a hot topic today. I kept referring to the discussion in pomegranate, so here it is.

Full Panel – June 9, 2020

DR. BELSITO: So this is Tris (Tetramethylhydroxypiperidinol) Citrate and we looked at the data, there was no DART data and no carcinogenicity but there was a negative 90-day dermal that appeared to be clear. It was felt that this really would not penetrate through skin. And, even though we did not have method of manufacturing or impurities, again we have the 90-day oral that was that was clean.

It's reported to be used as a photostabilizer. I was concerned about UV absorption, but Dan pointed out it really is a free radical quencher and that's how it stabilizes; it's not a sunscreen. So, if I've got this right I think we went safe as used.

DR. LIEBLER: Insufficient for method of manufacture and impurities.

DR. BELSITO: Okay, so we still wanted that despite the 90-day oral. Okay.

DR. LIEBLER: I mean we have nothing, so we always need something there.

DR. BELSITO: Okay.

DR. BERGFELD: So, insufficient rather than safe?

DR. BELSITO: Yeah, insufficient for method of manufacture and impurities.

DR. BERGFELD: Okay. Dr. Marks?

DR. MARKS: Thank you, Dan. I would have been very disappointed if you had let this slide without method of manufacture and impurities.

It's interesting, your team, and Dan, did you and Lisa talk ahead of time so you're on the same page about the photo? Because I raised -- aye, I see Lisa shaking her head no. Because I raised the same issue as a light stabilizer, do we need phototox data, does this absorb light? And, Ron Shank thought it probably structurally didn't. Lisa made the same comment that it is a light stabilizer because it sucks up free radicals. So, I guess I'll delete that need for phototox data, Don, if you're okay with that also then. We only need two data points for the insufficient data announcement.

DR. LIEBLER: We didn't have to talk about that; we have the tox chemist mind-melt thing going, so.

DR. BERGFELD: Floating through the air. So, you're seconding the motion of insufficient method of manufacture and impurities?

DR. MARKS: Yes. Second.

DR. BERGFELD: Any further discussion or comment regarding this motion and second? If not, I'm going to call the question. All those in favor of insufficiency for Tris Citrate, please raise your hands. Any of those opposing, please be verbal. Thank you. Unanimous approval of this activity. The next ingredient -- yes?

DR. MARKS: I'll just make one more comment. Preethi, I think it might be worthwhile noting in the discussion why we didn't need phototox data.

MS. RAJ: Okay, definitely.

DR. MARKS: And I know it's still an insufficient data announcement, but we'll eventually get to the discussion and I think it's important to state why we didn't feel we needed it.

MS. RAJ: Okay, noted, Dr. Mark. Thank you everyone.

DR. BERGFELD: Thank you. The next ingredient is Methicones, Dr. Marks.

DECEMBER 2020 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – December 7, 2020

DR. BELSITO: Okay. So we're moving on to the tris tetramethylhydroxypiperidinol. And at the last meeting in June -- or the meeting in June, not the last -- we decided to add in another ingredient, the oxide, which is a cosmetic ingredient, and also look at the nitroxide as a potential read across to give us data. Our major concern at that time was impurities. And I guess the issue is we have a 90-day dermal which is negative. And we also have a negative DART for the oxide. Does that help us with the issue of impurities?

DR. LIEBLER: Well, they didn't really address impurities even though we asked for it. I did look to see the commercially available compound, which would be the dianoxide I believe is 97 percent pure. So the one that you could buy from Sigma-Aldrich for example.

So I suspect that it's not the type of thing where purity is going to be an issue, where it's difficult to make this pure and keep it stable. And that's usually what we worry about, purity. In this case, even though we don't have it, I have at least that data point to suggest that it's probably not that much of a concern.

DR. BELSITO: All right. So then based upon that are we going with a conclusion, safe as used? We have manufacturing for the oxide but not for the other one that we added -- the original one, the tris(tetramethylhydroxypiperidinol) citrate.

DR. LIEBLER: Yeah.

DR. BELSITO: Do we need that, or are we assuming that it's just similar except for the citrate substitution instead of the oxide?

DR. LIEBLER: We really haven't gotten a response to our request for those data for either molecule. The description provided is a general synthesis method that is, I think, taken from the literature if I'm not mistaken.

MS. RAJ: Yes. That's correct, Dr. Liebler.

DR. LIEBLER: Yeah. In other words so we're basically getting a non-response. It's the citrate that has 388 uses. And we haven't really gotten a response on that one.

DR. BELSITO: Right.

DR. LIEBLER: And that bothers me. This is something that the provider should be able to provide the data on.

DR. EISENMANN: I have asked more than once.

DR. LIEBLER: Yeah. I know. No, I know. I'm sure you have. I think that we should have that information in our report. We can't really infer it from -- it's not obvious. I don't know how they make it. I don't know what contaminants would be. And therefore, I think that it's still insufficient.

DR. BELSITO: Okay. But we have a 90-day subchronic dermal on the citrate, 97.3 percent pure. However, there was no dose response here. So it was given at 50, 150, and 500 milligrams per kilogram of body weight. And it says that aberrations in glucose, urea, potassium concentrations in white blood cells were observed in animals given 50 and 500, but not the intermediate dose.

So it just makes me wonder about the adequacy of this study. Or was it just an anomaly that those animals happened to have those abnormalities and it doesn't really -- it's not a side effect of the drug -- or the ingredient, rather?

DR. SNYDER: Well, typically, a non-dose response would mean that it's not toxicologically significant.

DR. BELSITO: Right. So then does that mitigate our concerns with the 90-day dermal about the other endpoints? Or given what would -- because the DART study is on the oxide. Everything else is on the oxide.

DR. LIEBLER: I think the data for the oxide should be able to cover for the piperidinol and vice versa, if we add that up going either way. Because I think they would be metabolically pretty easily interconvertible. The oxide would be easily reduced to the alcohol metabolically.

DR. BELSITO: Okay. So we have DART on the oxide, and we have genotox on the oxide.

DR. LIEBLER: Yes.

DR. BELSITO: So is that adequate?

DR. LIEBLER: I think so.

DR. BELSITO: So then we're going safe as used?

DR. LIEBLER: Well, yeah. I mean, I personally don't like the lack of method of manufacture and impurities, where the information couldn't be reasonably inferred for this main ingredient. I don't think it's appropriate to go -- I don't think -- they clearly are insufficient on those two issues, even though based on the animal data it appears to be safe.

DR. BELSITO: Okay.

DR. LIEBLER: I have another issue with this report. It's not a major issue, but we're using this read across in several cases where -- I can't find a single case where we need the read across, where we don't already have sufficient data without the read across.

MS. RAJ: That was part of what we wanted to ask the panel collectively. We're still trying to standardize how we are approaching read across. So in this report as well as in -- I guess it was the glycerin ethoxylates, there was read across. So yeah, we would probably want some clarity on that.

DR. LIEBLER: So the first rule of read across is you only use it when you don't have data to support the endpoint. Even if you do have pretty good data for a read-across molecule that's similar, but you already have data from the ingredients that supports the endpoint, you don't touch the read across. So it's not like extra whip cream on top.

MS. RAJ: Okay.

DR. LIEBLER: Okay? In the case of the glycerin ethoxylates we had a data gap, where we had no DART, and so we had to go with the glycerin ethoxylate data -- or with the read-across analog data. Here we've got data in every case, and you can tell by looking at the tables. So if you've already got data, you don't need the read across. So I think we pull it out.

MS. RAJ: Okay. And also, I know we had talked briefly about the introductory read-across language wherever we use it, I guess, now. So would we want that introductory kind of read-across blurb or explanation for why we're using this data, wherever the read-across data appears? Or should it just maybe be summarized in the introduction and it kind of follows through the rest of the report -- or assumed, I should say?

DR. LIEBLER: Well, yeah. It's not really applicable to this report anymore because I think we're going to pull it out. But in the glycerin ethoxylates report, I think that's the format I prefer. It is the way we do it with the RIFM reports as well, which isn't necessarily the determinative for CIR. But I think it's helpful to standardize around that approach.

For every endpoint you briefly state what's inadequate about the data for the target, and why you're bringing in the read across. It's like two sentences. And you just put that in, in every instance where you introduce your read across, in the description of each endpoint. That's better than simply introducing it in the introduction and then only having an abbreviated version of justification in the table.

MS. RAJ: Okay. Thank you, Dr. Liebler, that's helpful. And how did the panel feel about the read-across table? Do you like the format and, I guess, how it's presented? That's Table 2, I believe.

DR. LIEBLER: Yeah.

DR. BELSITO: Well again, for this one we don't need the read across, but you're asking just in general, Preethi, correct?

MS. RAJ: Yeah. Yes.

DR. LIEBLER: Yeah. This is pretty much the same as what we had in the glycerin ethoxylate report. And I think the table format is okay.

MS. RAJ: Okay.

DR. LIEBLER: I mean, in principle there's a whole lot more information that could be brought into a read-across justification. So this is minimal. It's minimal and sufficient at this stage for CIR.

MS. RAJ: Okay.

DR. KLAASSEN: Maybe the title of the, well -- maybe -- I guess what I was thinking of was maybe we could -- instead of saying just chemical properties, we could say chemical properties of read-across chemical or chemicals.

DR. LIEBLER: I'm referring to table one.

MS. RAJ: Okay. But that table also includes tris citrate as well, right?

DR. BELSITO: Yes. It includes the two ingredients we're reviewing, and then it includes the nitroxide for the read across.

DR. LIEBLER: So again, the way we've done this in RIFM, which is pretty much is a more highly developed read-across justification strategy, we don't have the chemical properties of read-across ingredients mixed -- or read-across ingredients mixed up with those of the target ingredients.

MS. RAJ: Okay.

DR. LIEBLER: So the subjects of the report have their own chemical properties, Table 2, in this case.

And then in the read-across justification, we can expand the descriptions to include the chemical properties. And sometimes I could -- well in this case just to expand to include the chemical properties. But we don't want to mix them as they are in this version.

So we're going to take it out anyway for this report. I think we need a separate discussion -- maybe not just in the framework of this report -- on what's our ideal format for read-across presentation.

MS. RAJ: Yes. So yes, looking at the data profile. So from what you said, Dr. Liebler, since there is information for the original ingredient for all these endpoints, are we taking out data for the other two ingredients completely? Are we taking the substances themselves out of the report?

DR. LIEBLER: The read across.

DR. BELSITO: The read across is just nitroxide. The other two are the actual cosmetic ingredients, Preethi, right?

MS. RAJ: Right. Tris citrate and the oxide, the hydroxy tetramethylpiperidine oxide are the cosmetic ingredients. And then the third one is a non-cosmetic that we had --

DR. BELSITO: Right. So what Dan is saying, all the information on the tetramethylpiperidine nitroxide can be removed from this report because we have adequate data on the actual ingredients.

MS. RAJ: Okay. So both of the ingredients that we added can be removed it sounds like?

DR. LIEBLER: We only added one.

DR. BELSITO: I don't understand your question, we only added one.

MS. RAJ: Oh.

DR. BELSITO: And that stays.

MS. RAJ: Okay.

DR. BELSITO: We added the -- so originally, we were looking just as -- at the citrate. We added the oxide. The oxide stays. They're both cosmetic ingredients.

MS. RAJ: So you're removing the non-cosmetic ingredient?

DR. BELSITO: We're just removing the non-cosmetic, the nitroxide. We don't feel that we need that as read across. We have our datapoints made -- or we have sufficient data for our datapoints on the cosmetic ingredients themselves, we don't need a read across.

MS. RAJ: Okay. Thank you. Any changes in the distribution the panel would like to see?

DR. BELSITO: Well, I think that, as Dan said, we don't have manufacturing for the citrate. But we have that 90-day dermal, which was clean. There didn't seem to be any toxic effects on the dermal. And then we feel that the oxide is representative, and we have DART and genotoxicity on the oxide. And I don't think we need to belabor the point that it would be nice to get manufacturing and impurities on the lead ingredient, which is the most frequently used, but we don't have it. But we can get around it.

So I think just pointing out that, you know, we have a 90-day dermal on the citrate even though we don't have manufacturing and impurities gave us -- and it was supposedly 97.5 percent pure. And that gave us confidence and --

DR. LIEBLER: Don, I don't doubt the safety. But I have stuck to my guns on this issue of method of manufacture and impurities. And I'm even willing to accept relatively minimal information. But we've got nothing.

DR. BELSITO: So you think we should still go insufficient for that?

DR. LIEBLER: I do.

DR. SNYDER: I would push back on that a little bit because we have -- this is a significant systemic tox study. And it has a very nice, clean NOAEL. And this is only used at 0.05 percent leave-ons for the one, and 0.005 percent for the citrate.

And so we are miles away from cosmetic exposure, so I'm fine. If there was anything in there -- we're not getting any red flags anywhere, in either one of these, with quite a lot of tox data. So I would -- Curt, I don't know if you agree with that or not, but I doubt there's an impurity in there that's a bad player.

DR. LIEBLER: That's not where I'm coming from, Paul. I mean, I agree with you. And I also agree that stupid arguments often start with statements of principle. So I get that. As long as I've been on the panel, we have dinged ingredients for not having method of manufacture and impurities. I mean we're receiving nothing.

DR. SNYDER: Yeah. But generally, I think we also don't have very good systemic tox data in those instances, Dan. And so, therefore we're trying to see if there's any signal that might make us worry and then -- but this case we have, I think, adequate tox data, genotox, repro tox.

MS. RAJ: May I interject? So I think the second or third paragraph of the draft discussion, we do talk a little bit about the 90-day study that you all have been mentioning. Could we maybe add in there that there wasn't a dose response seen? And I know you had just said when there isn't a dose response, that that's not usually toxicologically significant?

DR. SNYDER: Well, no. The most important thing from the study, Preethi, is the fact that they come with a no observed adverse effect level.

MS. RAJ: Oh, yeah.

DR. SNYDER: And so, in this case it was 150 milligrams for any effect.

MS. RAJ: Okay.

DR. SNYDER: And so, to me that's the most important part. And yes, they did dose up to 500 and there were these quirky things. But when they clearly stated NOAEL, that's pretty solid data at where the toxicity is at. So that would probably be more relevant in this paragraph than not. So the NOAEL at 150 milligrams, that's what --

MS. RAJ: Okay. So I'll add that.

DR. SNYDER: Yeah.

DR. LIEBLER: So team, so I get from -- Paul, your point is well taken. I understand it. Don, I take it that you feel also that the tox data mitigate the need for method of manufacture and impurities. I'd like to hear what Curt thinks?

DR. KLAASSEN: Yes. I actually go along with Paul also.

DR. LIEBLER: Okay. All right guys, I defer to the expert judgement of my colleagues. And so, I will not hold this up for method of manufacture and impurities.

DR. BELSITO: Okay. So since this --

DR. LIEBLER: I will not filibuster.

DR. BELSITO: You will not filibuster, okay, thank you, Dan. Although we know you're from Tennessee.

DR. LIEBLER: Well, the senator from Tennessee are not even in the same galaxy so –

Cohen Team – December 7, 2020

DR. BERGFELD: You must have practiced it.

DR. PETERSON: Yeah. I'm very impressed.

DR. COHEN: You know. I think it's all that contact dermatitis work that's doing it. All right. It's Preethi. This is a draft tentative report. The Panel reviewed this in June of 2020 and approved adding data for the two proposed substances. The Hydroxy Tetramethylpiperidine Oxide was added as an additional cosmetic ingredient.

It's reported as a light stabilizer and antioxidant, with a max use of 0.05 percent in rinse off and 0.05 percent in leave on for the citrate. The oxide has a 12.5 percent in a nail product, but there's not use data available. I think we're still insufficient on method of manufacturing and impurities, but I'll let you comment further. Lisa, you want to start?

DR. PETERSON: Sure. So first of all, I want to say that the first two compounds are basically the same. One is a citrate salt of the first one. So they're basically -- you know, once they're in solution and in the body, they're basically the same thing. So, therefore, we don't need the read across, and I would delete the read across for this one, because it doesn't give you any data that you don't already have.

DR. SHANK: I agree.

DR. PETERSON: Where you look at all the Xs --

DR. COHEN: Good point.

DR. PETERSON: -- you don't need it, so I would remove it. And then Reference 6 seems to have a method of manufacturing for the (inaudible), you know, the not citrate one, I think. So there is a method of manufacture for that, but I would agree that's still missing method of manufacturing for the citrate and then the impurities for both of them. It would be nice to know what the impurities are.

DR. COHEN: Yeah. Ron?

DR. SHANK: Yes?

DR. COHEN: Any comments, thoughts?

DR. SHANK: No. You covered it perfectly. I had we need method of manufacture and impurities, and we don't need the read-across chemical because it doesn't contribute anything new. And no, it wouldn't --

DR. BERGFELD: Could I ask a question?

DR. SHANK: It's more likely to be absorbed faster than either of the cosmetic ingredients.

DR. COHEN: Yeah, Wilma.

DR. BERGFELD: The question I have is for Bart. Bart, is this one of the ingredients in our cosmetic ingredient chemical list? And if so, maybe we need to keep it because it gets rid of one?

DR. PETERSON: Or you could keep it from a structural point of view.

DR. BERGFELD: Yeah.

DR. PETERSON: It would fit in with these totally. So, if it's a cosmetic ingredient, I would leave it in and then talk about its own insufficiencies.

DR. HELDRETH: So the --

DR. PETERSON: Or then you could do some -- a little bit of read across, but I agree that the hydroxylated one would be -- there would be differences in absorption and metabolism and all that, once it got internal.

DR. HELDRETH: So the Hydroxy Tetramethylpiperidine Oxide and the Tris(tetramethylhydroxypiperidinol) Citrate are ingredients. The tetramethylpiperidine nitroxide is only added as a read-across source, it's not an ingredient.

DR. BERGFELD: Okay. Then delete it. Yeah.

DR. COHEN: So we can get rid of it?

DR. PETERSON: Yeah.

DR. SLAGA : Yeah.

DR. COHEN: Tom, anything further?

DR. SLAGA : Uh, no. I agree with we need the method of manufacturing and impurities, and that's it.

MS. RAJ: May I add, I think an IDA already went out for method of manufacturing and impurities for this report.

DR. SLAGA : Yeah. So no change.

DR. HELDRETH: That's right, Preethi. So then the next step would be to issue an insufficient data conclusion.

MS. RAJ: Okay.

DR. PETERSON: Well, there is -- Reference 6 does have a method of manufacture for the Hydroxy Tetramethylpiperidine Oxide. So we would just be missing impurities.

DR. COHEN: Okay. It needs to be put into the report. Question -- the modified --

DR. HELDRETH: If I might interject here.

DR. COHEN: What's that?

DR. HELDRETH: I just wanted to interject that that's a general methodology.

DR. PETERSON: Oh.

DR. HELDRETH: It wasn't necessarily specific to cosmetic ingredients.

DR. PETERSON: Oh. Okay. Never mind then.

DR. BERGFELD: Yeah.

DR. COHEN: There was 104 human subjects in a modified Draize test up to 0.5 percent, and there's concentration of use in the nail product at 12 percent. And it's not uncommon for nail product, even when they're wet, to be transferred up to the face, the eyelids, the neck, and lips.

Do we need HRIPTs on higher concentrations? I mean, the nail's an interesting issue here, right, because it -- I'm not so worried about that much penetration through the nail but rather transfer. I just would be interested in your thoughts. Ron, Tom, any thoughts?

DR. SHANK: Well, how does the chemical applied to the nail get to the lips and to other tissues?

DR. BERGFELD: By movement.

DR. SHANK: Movement?

DR. COHEN: In the old days when there was a lot of tosylamide formaldehyde resin in nail polish, it was a common cause of eyelid dermatitis. So people put their fingers up on their face all the time and don't always wait 'til it fully cures, which could be quite some time. It's a big difference in the concentration, so I just wanted to know if this had come up before for nail products.

DR. PETERSON: So you mean the example of formaldehyde is that it's a volatile chemical, and these compounds, I don't think, are volatile. But it could come off, I guess. But you're worried about volatilization?

DR. COHEN: No. Just touching.

DR. BERGFELD: But you said it was uncured. It was uncured, so you could handle in the discussion as the nail product had to be dry or cured.

DR. COHEN: Yeah, I think that's okay, that we should handle that in the discussion, Preethi, about transference of wet or uncured nail product onto glabrous skin --

MS. RAJ: Okay.

DR. COHEN: -- because the current data of that 0.5 percent.

MS. RAJ: Okay. I think I missed the term you said for skin. Did you say gla- --

DR. COHEN: Glabrous. You could just use skin. Skin's okay.

MS. RAJ: Okay.

DR. COHEN: And I know it came up at the last meeting, again, so there's no chromophore here, and it's acting as an antioxidant through radical trapping is from what came up.

DR. PETERSON: Yep.

DR. COHEN: Any issue of concern during its trapping that there's any confirmational change that could interact with proteins in any way?

DR. PETERSON: So these compounds are used to study radicals and experiment in the lab. And so, the radicals that are formed are quite stable in comparison to the radicals that they're trapping. So I don't -- because they are so -- they're a stable trap. I don't know.

DR. COHEN: Look, do you have --

DR. PETERSON: But they're still radical, so I mean, they trap it.

DR. COHEN: -- do you remain unconcerned about them?

DR. PETERSON: Yeah, I think the discussion we had last time we talked about this was appropriate. You know, there's no great -- I don't know.

DR. COHEN: Okay.

DR. PETERSON: I think that it would come up with the dermal sensitization or irritation, or something like that, that you would see it.

DR. COHEN: Well, (inaudible).

DR. PETERSON: But, again, that's a presumption on my part, so I don't really know.

DR. COHEN: It's in the assumption of photo irradiation, not just routine dermal sensitization studies. Okay. So, we have an insufficient data conclusion on it for now.

DR. PETERSON: I mean, if you want to put phototox in there, but I don't --

DR. COHEN: And we want --

DR. PETERSON: You can always ask for it, but I don't know.

DR. COHEN: All right.

MS. RAJ: Does the Panel have any changes for the discussion?

DR. SHANK: No.

MS. RAJ: Okay.

DR. SLAGA : Not here either.

MS. RAJ: Okay. Thank you.

DR. SHANK: Well, yes. Remove the read across.

MS. RAJ: Yeah.

DR. PETERSON: Yeah, remove the read across.

MS. RAJ: Okay. The non-cosmetic ingredient?

MR. GREMILLION: Sorry, um --

DR. COHEN: Tom?

MR. GREMILLION: I see there's -- you can call me Thomas just to --

DR. COHEN: I'm sorry. I'm sorry. Yeah, otherwise, we won't know which one it is.

MR. GREMILLION: Exact- -- and I -- yeah, and I go by Thomas. But I noticed that the inhalation boilerplate is in here. Is this in products that are aerosolized? And then if it is, does the ocular irritation data come into play?

DR. PETERSON: Yeah, there is a potential for inhalation.

MS. RAJ: I think -- well, the -- I'm trying to see here.

DR. HELDRETH: Yeah, there's potential for inhalation with the citrate up to 0.01 percent.

MS. RAJ: Yeah, in colognes and toilet waters, it's there at 0.05 percent, I believe.

MR. GREMILLION: Okay. So the citrate wasn't the one that was so irrita- -- that was so terrible for the eyes or that acute? Okay. That's a pretty small --

DR. COHEN: But I think at some point there was -- the oxide had some -- both of them had some ocular tox, but the oxide had some fair ocular toxicity, right?

MR. GREMILLION: That's what I was looking at.

DR. COHEN: Yeah. And, by the way, was the subject of my comments a little earlier about, "formulated to be nonirritating for the eye." I mean, this is another example of this -- running into that same quandary.

MS. RAJ: So I actually looked at the ocular studies for the data that we added, Dr. Cohen. And in the first study for the oxide, the eyes were washed. But, in the second study, the eyes were not washed. There was just a control eye, I guess, like the other eye was used as a control. And yeah, we don't have the concentration of use for those ingredients.

DR. BERGFELD: Did we delete the oxide? That was not the read across one?

DR. SHANK: No, the nitrite -- the nitric oxide was the read across.

MS. RAJ: Yeah.

DR. BERGFELD: Not the oxide?

DR. SHANK: Right.

DR. COHEN: No, it was the nitroxide that was deleted.

DR. PETERSON: But the ocular irritation is all of either the Hydroxy Tetramethylpiperidine Oxide or the citrate.

DR. COHEN: Yeah. So is anyone interested or concerned about adding a "formulate to be nonirritating" because of that, or is that not something that people are considering?

DR. BERGFELD: These chemicals were undiluted. Most of them are irritated when they're undiluted?

DR. COHEN: Yeah. Okay. Yeah, so I don't have as much experience with these Category 1 substances. I don't know how frequent that comes up for ocular toxicity.

DR. BERGFELD: Certainly, one would use undiluted.

DR. COHEN: Yeah. All right. So we have an insufficient data conclusion. I have what the group has suggested. And any other questions or comments before we move on?

DR. SHANK: No.

DR. BERGFELD: Only to say in your discussion, you need to delete all the read-across stuff. There is one in the first paragraph, and I guess that would be the second paragraph -- third paragraph.

MS. RAJ: And just to understand, is the main reason for the insufficient data conclusion because of the method of manufacture and impurities?

DR. PETERSON: Yep.

DR. COHEN: Yes, and we were considering phototox on it.

MS. RAJ: Is that even -- even when citrate doesn't have a chromophore, is that still concerning?

DR. BERGFELD: No.

DR. COHEN: Well, that was part of the report.

DR. SLAGA : It shouldn't have been.

DR. COHEN: Say that again, Tom.

DR. PETERSON: It's not -- itself is not going to absorb UV to form something that's toxic, so you know --

DR. COHEN: I think that was the point of my question before. Then I'm okay leaving it as is. So, yes, it's on method of manufacturing and impurities.

MS. RAJ: Okay. Thank you.

DR. COHEN: Okay. I think we're at our last one: Portulaca oleracea.

Full Panel – December 8, 2020

DR. COHEN: Okay, so this is a draft tentative report for HydroxyTetramethylpiperidine Oxide and TrisTetramethylhydroxypiperidinol Citrate. And we reviewed this in June of 2020, and the oxide was added as an additional ingredient. They're used as light stabilizers and anti-oxidants. Max used, so 0.05 in rinse-off and 0.05 in leave on. And the oxide is in 12.5 percent in the nail product, although, we didn't have much use data for the oxide. Our conclusion was an insufficient data conclusion. We need methods of manufacturing and impurities. And there was also a suggestion to delete tetramethylpiperidine nitroxide as it didn't add any additional information.

DR. BERGFELD: Is that a motion?

DR. COHEN: Yes.

DR. BERGFELD: Is there a second?

DR. BELSITO: Manufacturing and impurities for which ingredients?

DR. COHEN: Sorry, for the oxide.

DR. BELSITO: Okay, but we -- for the oxide -- we have a 90-day dermal for the oxide. We have a DART for the oxide. We have a genotox and a statement of presumed lack of absorption. So, what are you concerned about with all that additional systemic tox data?

DR. BERGFELD: Lisa, or Tom?

DR. PETERSON: I think you have a case of, you know, i-dotting and t-crossing. So, if that is the history of the panel to say, you know, we don't need it because the compound basically says that it's safe, then I'm okay with that. I think -- and my team -- the tox -- you know, it's just there is no method of manufacture for the citrate. And there a generic for the --

DR. COHEN: For the citrate, I'm --

DR. PETERSON: For the oxide, there's generic. And in our discussion it seemed to come out that everybody said that, yeah, it was insufficient. So, that's why we ended up in that point.

But I think if, you know, again, it gets to what is the importance of all the information? And if the importance of the information is to prove that it's safe, and that there're no toxic impurities, and everybody is able to rely on the toxicity data to say there's nothing of concern, then that's okay.

I mean, it's a preponderance of data suggest that it's safe. I mean, I don't have any big concerns. And I think --

DR. COHEN: I think -- Lisa, you corrected me, I think, correctly. It was the citrate, not the oxide, correct?

DR. SNYDER: That's correct. So, Lisa, we typically take all of the data to make our interpretation and conclusions. So in this case we have a leave-on concentration of use for the citrate, .005 percent. We have a 90-day dermal that was tested up to 500 milligrams. It was a no observed adverse effect -- well, 150 milligrams. So, that would suggest there's nothing there of concern. So that's why our team felt it was okay to go ahead and clear that ingredient as safe as used.

DR. PETERSON: Right, so, and I would support that assuming my team, you know, if people on my team agreed with that.

DR. LIEBLER: Lisa, this is Dan. I was sympathetic to your point of view, but my teammates were not convinced of that, so.

DR. PETERSON: Okay, well, I think my team, Ron and Tom need to respond and I'll go with them.

DR. BERGFELD: Please, Tom first then Ron.

DR. SLAGA: Yeah, I think it's okay. I would go with safe.

DR. BERGFELD: Ron?

DR. SHANK: Is very interesting conversation. Our team has long supported using toxicology data as, if you have a lot of toxicology data and there are no concerns, you don't need the methods of manufacture and impurities. But the Belsito team has long argued you need that information.

DR. PETERSON: Yeah, and I was going to say --

DR. SHANK: For a complete.

DR. PETERSON: Yeah. And, because Dan -- I'm always like well, Dan always insists on this method of manufacturing.

DR. SHANK: Right.

DR. PETERSON: So, well, therefore we're going to -- we don't have it, so --

DR. LIEBLER: It just shows --

DR. SHANK: I don't think you need it.

DR. LIEBLER: My guess is for me to put on one of Ron's Shanks' shirts, what can I say?

DR. COHEN: I --

DR. BERGFELD: It's not like we don't need it. David?

DR. COHEN: Well, again, I'm chucking this up to my novice point of view here. But can we rely on the tox data that we have for any and all impurities? I just don't expect we may see everything there, and it's completely blank in this report.

DR. BERGFELD: Ron?

DR. SHANK: Let me check. What is completely blank? We have a lot of tox data.

DR. COHEN: Impurities.

DR. SLAGA: Impurities.

DR. COHEN: Impurities.

DR. BERGFELD: Impurities.

DR. BELSITO: But we have a 90-day oral on the citrate; it was clean.

MS. RAJ: I think that's a dermal --

DR. BELSITO: We never said -- no, it was oral. And the NOAEL was 100 mg/kg per body weight, huge. This is Page 18 in the PDF.

DR. PETERSON: There's a couple of --

DR. BELSITO: And then we have a dermal where it's 150 mg/kg per body weight.

DR. BERGFELD: Ron, then Carol, then Tom.

DR. BELSITO: I'm sorry, the oral was 28-days, dermal was 90.

DR. SHANK: Yeah.

DR. BELSITO: I mean, we typically used dermal to clear impurities and other data needs.

DR. LIEBLER: You know, if I don't insist on it now I'll never be able to insist on it again. I apologize to my teammates, who I respect. And in my kumbaya sprit yesterday I went along with agreeing to a blank, as David just put it. Thank you, David, for the spine stiffener. I can't wear Ron Shanks' shirt any longer. I think this is insufficient for method of manufacturing and impurities, period.

DR. BERGFELD: Okay. How about Tom responding and then I'm going to go to Carol -- and Tom, Thomas.

DR. SLAGA: Well, I go with Ron in that if you have sufficient toxicological data, if there is some impurity in there it's (audio skip) doing anything. So it's safe.

DR. BERGFELD: Okay.

DR. SLAGA: I mean, what --

DR. SHANK: You have genotox on both ingredients. You have irritation and sensitization on both ingredients. You have ocular on both ingredients. If there was a bad actor, impurity, the tox studies should have --

DR. SLAGA: Would show it.

DR. SHANK: -- show it.

DR. LIEBLER: Yeah, this looks --

DR. SHANK: This is an argument we've had every time.

DR. LIEBLER: Right. And I haven't changed.

DR. SHANK: And I just entertain it. So --

DR. LIEBLER: I waivered (audio skip) change.

DR. SHANK: -- we'll put that in, Dr. Liebler, so that you would be happy.

DR. LIEBLER: So if you don't like it vote me down.

DR. BERGFELD: Okay.

DR. BELSITO: We're going to.

DR. BERGFELD: We need to have some other people come in, Carol?

DR. EISENMANN: I just want to know, in this case at least for the studies that were done the purity of the material tested was stated, so it was like 97 percent pure. So, your conclusion is for the material that was tested. I don't know if that helps any.

DR. BERGFELD: Okay.

DR. SHANK: Always, yes.

DR. SLAGA: Yes.

DR. COHEN: Yes.

DR. BERGFELD: Thomas?

DR. GREMILLION: Is it relevant that the -- so it's the citrate that you don't have the method of manufacturing for, if I understand correctly. And that's also the ingredient that's not irritating to the eye. And I just wonder if that inform this discussion. Maybe I'm misunderstanding how method of manufacturing helps inform the analysis.

DR. BELSITO: Tomas, I --

DR. GREMILLION: It's a Category I substance. These other two are Category I substances for causing damage to the eye.

DR. BERGFELD: Dr. Cohen, you want to respond?

DR. COHEN: I certainly understand the point. I think, if you had method of manufacturing, perhaps you can make inferences from there, or if you had impurities you could make inferences from not having method of manufacturing. But you don't have either for that.

And if there're not that important then we don't need them for anything, right. We could just go straight to dermal irritation. I'm not trying to be cheeky by saying that. I'm trying to read through the report and say why am I giving it a pass, because I'm (inaudible) to the dermal irritation and tox data.

DR. SNYDER: One of the hardest lessons I had when I joined the committee was understanding the thought process of the panel; in that you cannot create a checkbox list for every ingredient and go down the checkbox and check all the boxes and say safe as used, because it's a summation of all of the data.

In this case, as I (audio skip) we have a very, very low level of use, .005 percent for the citrate. We have tremendous tox data on a citrate. We have oral 28-day, we have a 90-day dermal; we oftentimes don't even have a 28-day dermal. In this case we have what I consider to be more than sufficient tox data to support safety of this ingredient.

And then, also, we have the other, the oxide, we have sufficient impurities and method of manufacture and tox data. So, it would be -- there would -- certainly something would show up in the tox data, for the citrate, if the impurities were substantially different from the tox, in my opinion.

DR. BERGFELD: Curt, can I call on you?

DR. SLAGA: Well stated, Paul.

DR. SHANK: Well stated.

DR. BERGFELD: Yeah. Curt?

DR. KLAASSEN: Yes, I'd like to go along with everything that Paul said, Tom said, and Ron said. That the toxicology data here is so overwhelming that we don't need the methods of manufacture.

DR. BERGFELD: Dr. Cohen, did you want to restate your conclusion then, or do you want to rescind it?

DR. COHEN: I think it's moving information. Lisa, do you have any further --

DR. BERGFELD: You can always discuss it.

DR. COHEN: Huh? Yeah, okay.

DR. BERGFELD: You can always put it in the discussion.

DR. COHEN: The motion is safe --

DR. BERGFELD: It's --

DR. COHEN: -- in the present practice and concentration.

DR. BERGFELD: Okay. Don, are you seconding that?

DR. BELSITO: Yeah, I'll second it. And the only other thing I want to mention is that we did not feel we needed the data from Tetramethylpiperdine nitroxide to clear this. It was originally brought in, but we would recommend that that data be removed from the report.

DR. BERGFELD: Is that agreeable.

DR. SHANK: I agree.

DR. COHEN: Yeah, that was in the original motion.

DR. LIEBLER: Yeah, the point to underscore about the read-across is, the first rule of read-across is that you only do it when you have a data gap that can't be filled in another way. And this was just sort of thrown in as extra data. And we should avoid doing that in future reports.

DR. BERGFELD: Okay.

DR. COHEN: Can I ask a question for Don?

DR. BERGFELD: absolutely.

DR. COHEN: Don, the nail product reported 12.5 percent concentration. Did you have any issues or concerns with ectopic application in the (inaudible) application of product on the face, eyelids?

DR. BELSITO: No, not really. No. Not with this particular product.

DR. COHEN: Okay.

DR. BELSITO: Right, because we're not seeing any (audio skip).

DR. COHEN: Okay.

DR. BERGFELD: Any other comments? We have some discussion to entertain regarding the lack of methods and impurities, which can be added. And, I think the removal of one of the current chemicals that was in read-across.

May I call the question? Anyone else have anything to say? All right, I'm going to call the question. Anyone oppose to a safe conclusion, with a discussion as stated previously? Hearing none unanimously approved as safe. Moving forward then.

The next ingredient in this list is a botanical, Dr. Belsito presenting, Portulaca oleracea, I guess it's pronounced.

Safety Assessment of Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate as Used in Cosmetics

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

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

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate as used in cosmetic formulations. These ingredients are reported to function as an antioxidant and a light stabilizer, respectively. The Panel considered the available data and concluded that Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate are safe as used in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This is a safety assessment of Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Hydroxy Tetramethylpiperidine Oxide is reported to function as an antioxidant, and Tris(Tetramethylhydroxypiperidinol) Citrate is reported to function as a light stabilizer, in cosmetics.[1] In 2014, the Expert Panel for Cosmetic Ingredient Safety (Panel) published a safety assessment of a related ingredient, citric acid, and 32 inorganic citric acid salts and alkyl citrate esters, concluding that these ingredients are safe in the present practices of use and concentration in cosmetics.[2]

Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate are structurally related as piperidine nitroxides. Therefore, these cosmetic ingredients have been reviewed together in this assessment.

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 Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[3,4] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definition and Structure

Hydroxy Tetramethylpiperidine Oxide (CAS No. 2226-96-2) is an organic compound and Tris(Tetramethylhydroxy-piperidinol) Citrate (CAS No. 220410-74-2) is a salt. These piperidine nitroxides conform to the structures shown in Figures 1 and 2, respectively.[1]

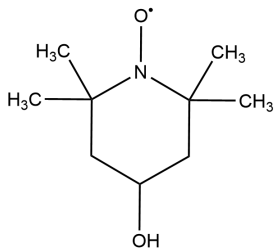

Figure 1. Hydroxy Tetramethylpiperidine Oxide

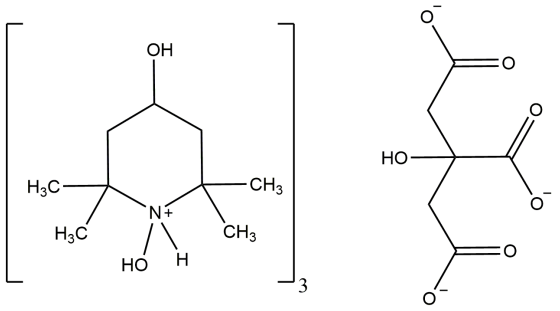

Figure 2. Tris(Tetramethylhydroxypiperidinol) Citrate

Chemical Properties

Hydroxy Tetramethylpiperidine Oxide has a formula weight of 172.24 g/mol and an estimated log P_{ow} of 0.56,[3] while Tris(Tetramethylhydroxypiperidinol) Citrate has a formula weight of 711.9 g/mol and a log P_{ow} of -0.29.[4] Both are soluble in water. The chemical properties of these cosmetic ingredients are further outlined in Table 1.

Method of Manufacture

A general synthesis mechanism for Hydroxy Tetramethylpiperidine Oxide involves derivation from triacetoneamine.[5] Method of manufacture data were not found, or received, for Tris(Tetramethylhydroxypiperidinol) Citrate.

Impurities

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

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics is 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 Council, of maximum reported use concentrations by product category.

Frequency of use data were not available for Hydroxy Tetramethylpiperidine Oxide in the VCRP;[6] however, according to a concentration of use survey conducted by the Council in 2020, this ingredient is reported to be used in nail formulations, at a maximum concentration of 0.019% in basecoats and undercoats.[7] According to 2021 VCRP data, Tris(Tetramethylhydroxy-piperidinol) Citrate is reported to be used in 125 cosmetic formulations, most of which are leave-on formulations (111 uses; Table 2).[6] The results of the concentration of use survey conducted by the Council in 2018 indicate that the maximum use concentration of this ingredient in leave-on dermal products is 0.05% in cologne and toilet waters.[8]

Tris(Tetramethylhydroxypiperidinol) Citrate is used in formulations applied to the eye area, at up to 0.005% in eye lotions. It is also used in products which allow for mucous membrane exposure, such as in bath soaps and detergents, at reported maximum concentrations of 0.05%.

Additionally, Tris(Tetramethylhydroxypiperidinol) Citrate is used in cosmetic sprays and could possibly be inhaled; for example, Tris(Tetramethylhydroxypiperidinol) Citrate is reported to be used up to 0.05% in cologne and toilet waters. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[9, 10] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[11, 12]

Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate are not restricted from use in any way under the rules governing cosmetic products in the European Union.[13]

Non-Cosmetic

Data for the non-cosmetic use of Tris(Tetramethylhydroxypiperidinol) Citrate were not found. Clinically, Hydroxy Tetramethylpiperidine Oxide has been noted for its potential to function as a nitroxide, to provide protection against radiation and oxidative stresses, both in vitro and in vivo.[14]

TOXICOKINETIC STUDIES

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

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute dermal, oral, and inhalation toxicity studies summarized below are described in Table 3.

The dermal LD_{50} of Hydroxy Tetramethylpiperidine Oxide was determined to be > 2000 mg/kg bw in male and female Sprague-Dawley rats.[3] The dermal LD_{50} of Tris(Tetramethylhydroxypiperidinol) Citrate was determined to be > 2136 mg/kg bw in male and female New Zealand white rabbits.[4]

The oral LD_{50} of Hydroxy Tetramethylpiperidine Oxide was determined to be 953 mg/kg bw in males, 1115 mg/kg bw in females, and 1053 mg/kg bw in both sexes (combined) in Tif/RAIf rats.[3] In an acute oral toxicity study of Tris(Tetramethyl-hydroxypiperidinol) Citrate, the LD_{50} was determined to be 2495 mg/kg bw in males, between 1068 and 1602 mg/kg bw in females, and 1758 mg/kg bw in both sexes (combined) in Sprague-Dawley rats.[4]

In an acute inhalation study, performed in accordance with Organisation for Economic Co-operation and Development test guideline (OECD TG) 403, no mortality or gross abnormalities occurred when male and female Sprague-Dawley rats were exposed (nose-only) to aerosolized Tris(Tetramethylhydroxypiperidinol) Citrate, at a concentration of 5.08 mg/l, with a mass median aerodynamic diameter (MMAD) of 3.8 µm, for 4 h.[4] The LC_{50} was determined to be > 5.08 mg/l.

Short-Term Toxicity Studies

Oral

Hydroxy Tetramethylpiperidine Oxide

In accordance with OECD TG 407, groups of 6 male and 6 female Sprague-Dawley rats were administered 0 (vehicle; water), 8, 40, 200, or 1000 mg/kg bw/d Hydroxy Tetramethylpiperidine Oxide, via gavage for 28 d, and then killed.[3] Two additional recovery groups, consisting of 6 males and 6 females that were administered either the vehicle or the highest dose, were kept alive and observed for 14 d after treatment. No mortality occurred and no abnormalities were reported during the recovery period. In the normal test groups, salivation was observed in all animals in the 1000 mg/kg group at varied timepoints of dosing, and in 1 male in the 200 mg/kg group towards the end of dosing. Males and females in the high dose group exhibited a decrease in blood cell count and hemoglobin, which persisted during the recovery period. Spleen and liver weights were increased in both sexes for the 1000 mg/kg group as well, but only persisted in females during recovery. Blackened spleens were noted in both sexes of the 1000 mg/kg/d group, and was reversible upon recovery. Upon necropsy, a dose-dependent increase in congestion and hemosiderin-laden cells in the spleen and hepatocyte swelling was observed in the 200 mg/kg females, and both sexes in the 1000 mg/kg group. The no-observed-adverse-effect-level (NOAEL) was determined to be 40 mg/kg bw/d, under the conditions of this study.

Tris(Tetramethylhydroxypiperidinol) Citrate

In accordance with OECD TG 407, groups of 5 male and 5 female Sprague-Dawley rats were exposed to 0 (vehicle; water), 100 (low), 500 (mid), or 1000 (high-dose) mg/kg bw/d Tris(Tetramethylhydroxypiperidinol) Citrate in deionized water via gavage for 28 d , and then killed.[4] Two additional groups of 5 males and 5 females were dosed with 0 or 1000 mg/kg/d for 28 d, and then observed post-exposure for 14 d, serving as recovery groups. No mortality occurred during the study. Dose-dependent abnormalities, such as salivation and apparent blood around the facial area, neck and forelimbs, were identified in the males and females dosed with 500 and 1000 mg/kg bw/d. Clinical pathology findings showed a slight increase of serum bilirubin in high-dose male rats, and a statistically significant slight decrease in red blood cell counts (except in mid-dose animals), hemoglobin, and hematocrit in females. Spleen weights were increased in the mid- and high-dose male rats, and there was a minimal to mild increase in the congestion of red pulp of the spleen in several of the male and female rats of the high-dose group. These effects were reversible during the recovery period. The no-observed-effect-level (NOEL) was determined to be 100 mg/kg bw/d.

Subchronic Toxicity Studies

Dermal

Tris(Tetramethylhydroxypiperidinol) Citrate

The dermal toxicity of Tris(Tetramethylhydroxypiperidinol) Citrate (97.3% pure) was evaluated in a 90-d study in Wistar Han rats, in accordance with OECD TG 411.[4] The test substance was administered as a suspension in 0.5% carboxymethylcellulose aqueous solution, and open applications of 0, 50, 150, or 500 mg/kg bw/d were made to the clipped skin of groups of 10 male and 10 female rats. The coverage area was approximately 10% of body surface area (i.e., 45 – 50 cm^2 in males and 30 – 35 cm^2 in females). The animals were killed at the termination of dosing. An additional two groups of 5 males and 5 females received open applications of 0 or 500 mg/kg bw/d of the test substance for 13 wk, and were observed for 4 wk post-dosing as recovery animals. The application sites were not wiped after dosing, and were only cleaned in the instance

of excess residue with purified water; ingestion was not prevented. There were no premature deaths. Scabs were noted at the application site during dosing in 2/15 males and 3/15 females dosed with 500 mg/kg bw/d and 1/10 females in both the 50 and 150 mg/kg bw/d. Chorioretinopathy, noted in 2 males and 1 female dosed with 500 mg/kg bw/d, was considered age- and strain-related, and not a test article-related adverse effect. Aberrations in glucose, urea, and potassium concentrations and white blood cell count were also observed in animals given 50 and 500 mg/kg bw/d. The effect on glucose and urea were reversible; however, the effects on white blood cell count and potassium concentrations persisted. An increase in spleen weight and congestion was observed in males and females, but similar congestion was observed in the controls, and the increased weight was reversed in the 500 mg/kg bw/d group of animals following the recovery period. Minimal acanthosis of the epidermis occurred in males and females across all dosing groups, however, it was considered negligible due to similarities in controls. Based on the results of this study, the NOAEL for cutaneous application of the test substance was determined to be 150 mg/kg bw/d.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Hydroxy Tetramethylpiperidine Oxide

In accordance with OECD TG 414, groups of 22 female Wistar rats were used to evaluate the effects of Hydroxy Tetramethylpiperidine Oxide upon maternal toxicity, as well as embryonic and fetal development.[3] Mated dams were dosed from day 6 to 21 of gestation, via gavage, with 0, 40, 125, or 400 mg/kg bw/d of 98.4 % Hydroxy Tetramethylpiperidine Oxide, in polyethylene glycol. Body weight, appearance and behavioral changes were determined daily during pregnancy, and dams were killed on day 21 of gestation. Mouth rubbing, salivation, and paddling, observed upon immediate administration, and stained fur and minimal sores were considered incidental and not related to the test substance. No adverse effects on maternal reproductive parameters, body weight, food consumption, and post-mortem findings were observed. Several statistically significant changes were observed in the 400 mg/kg dams, including increases in hemoglobin, red blood cell, and reticulocyte count, accompanied by relative increases in spleen weights and aspartate and alanine aminotransferase activity. Kidney dilation, noted in litters from all groups, was statistically significant in the litters of the 400 mg/kg dams; however, in the absence of a dose-response relationship, was not considered toxicologically significant. The NOAEL was determined to be 125 mg/kg/d for maternal toxicity, and 400 mg/kg/d for fetal toxicity.

GENOTOXICITY STUDIES

Details of the genotoxicity studies summarized below are described in Table 4.

In a bacterial reverse mutation assay, Hydroxy Tetramethylpiperidine Oxide was weakly mutagenic when tested at up to 5000 µg/plate in *Salmonella typhimurium* strains TA 100 and 1537, in the presence of metabolic activation.[3] In an Ames test, Tris(Tetramethylhydroxypiperidinol) Citrate did not cause an increase in the mean number of revertants per plate in strains of *S. typhimurium* and *Escherichia coli* WP2 uvr A, when tested at up to 5000 µg/plate, either in the presence or absence of metabolic activation.[4] In a chromosomal aberration test of Tris(Tetramethylhydroxypiperidinol) Citrate tested at up to 5000 µg/plate in Chinese hamster ovary (CHO) cells, there was a weak increase of cell aberrations at the highest dose, in the non-activation assay, and the test substance was not considered genotoxic.[4]

In vivo micronucleus tests were performed with mice. No genotoxicity was observed with 1200 mg/kg bw Hydroxy Tetramethylpiperidine Oxide (administered by gavage),[3] or with up to 200 mg/kg Tris(Tetramethylhydroxypiperidinol) Citrate (administered intravenously).[4]

CARCINOGENICITY STUDIES

No carcinogenicity studies were found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION

The dermal irritation and sensitization studies summarized below are described in Table 5.

Hydroxy Tetramethylpiperidine Oxide, at a dose of 0.5 g, did not cause dermal irritation when applied semi-occlusively to male Klein Weisse Russen rabbits for 4 h, and did not cause sensitization in Pirbright Dunkin-Hartley guinea pigs, tested at the same dose, in a Buehler test.[3] Tris(Tetramethylhydroxypiperidinol) Citrate was deemed non-irritating when applied to male and female New Zealand white rabbits for 4 h at a dose of 0.5 g using a semi-occlusive patch, and, non-sensitizing when tested, undiluted, in male and female Hartley albino guinea pigs in a maximization test.[4]

In a modified Draize test, up to 0.5% Tris(Tetramethylhydroxypiperidinol) Citrate was dermally tested in 104 human subjects. Adverse events were considered unrelated, and the test substance was deemed non-sensitizing.[4]

OCULAR IRRITATION STUDIES

Animal

Hydroxy Tetramethylpiperidine Oxide

The ocular irritation potential of Hydroxy Tetramethylpiperidine Oxide was evaluated in the eyes of 3 male Klein Weisse Russen rabbits, in accordance with OECD TG 405.[3] An undiluted dose of 0.1 g Hydroxy Tetramethylpiperidine Oxide was instilled into the eye (control not used) for 24 h, after which it was washed with saline. The treated eyes were scored after 24, 48, and 72 h of exposure. Due to an average conjunctiva score of 2.67 (out of 3 max score), average chemosis score of 2 (out of a 4-max score), and 5 of the 12 scored reactions being irreversible, the test material was deemed a Category 1 substance, causing serious and irreversible damage to the eye.

Tris(Tetramethylhydroxypiperidinol) Citrate

The ocular irritation potential of Tris(Tetramethylhydroxypiperidinol) Citrate (93.64% pure) was evaluated in the eyes of 3 female New Zealand White rabbits, in accordance to OECD TG 405.[4] Each rabbit received a 0.027 g (0.1 ml weight equivalent) dose of the undiluted test article, instilled into the conjunctival sac of the right eye, while the other eye remained untreated and served as the corresponding control for each animal. Test and control eyes were examined for signs of irritation for up to 10 d following dosing. The mean irritation score was 0.78 (maximum score of 3), and irritation was fully reversible 72 h to 10 d after exposure. Based on EC Regulation No 1272/2008 (CLP) criteria, the test item was considered non-irritating to rabbit eyes.

SUMMARY

According to the *Dictionary*, Hydroxy Tetramethylpiperidine Oxide is reported to function as an antioxidant, while Tris(Tetramethylhydroxypiperidinol) Citrate is reported to function as a light stabilizer, in cosmetics. In 2021, VCRP data were not available for Hydroxy Tetramethylpiperidine Oxide; Tris(Tetramethylhydroxypiperidinol) Citrate was reported to be used in 125 formulations. According to Council survey data, Hydroxy Tetramethylpiperidine Oxide is reported to be used at a maximum concentration of 0.019% in bases and undercoats (2020), and Tris(Tetramethylhydroxypiperidinol) Citrate at 0.05%, with the highest reported concentration of use reported for cologne and toilet waters and in bath soaps and detergents (2018).

The dermal LD_{50} of Hydroxy Tetramethylpiperidine Oxide was determined to be > 2000 mg/kg bw, in 10 Sprague-Dawley rats exposed to an occlusive patch of 2000 mg/kg bw for 24 h. In an acute dermal toxicity study, 10 New Zealand white rabbits were exposed to an occlusive patch of up to 2136 mg/kg bw of Tris(Tetramethylhydroxypiperidinol) Citrate for 24 h. The dermal LD_{50} was determined to be > 2136 mg/kg bw.

In an acute oral toxicity study, groups of 5 Tif/RAIf rats received 500, 1000, 2000, or 5000 mg/kg bw Hydroxy Tetramethylpiperidine Oxide, via gavage. No mortality occurred in the 500 mg/kg group. Three males and 1 female died in the 1000 mg/kg group, while all males and females died in the 2000 mg/kg and 5000 mg/kg groups. The oral LD_{50} for both sexes (combined) was determined to be 1053 mg/kg bw. In an acute oral toxicity study, groups of 5 Sprague-Dawley rats received up to 3204 mg/kg bw (highest male dose) and 2136 mg/kg bw (highest female dose) of Tris(Tetramethylhydroxypiperidinol) Citrate, by gavage. Three males and 2 females that received the highest dose died prior to scheduled necropsy. The oral LD_{50} for both sexes (combined) was determined to be 1758 mg/kg bw.

In an acute inhalation toxicity study, 10 Sprague-Dawley rats were exposed to aerosolized 94.8% pure Tris(Tetramethyl-hydroxypiperidinol) Citrate (estimated MMAD 3.8 µm), at a concentration of 5.08 mg/L, nose-only, for 4 h. The acute inhalation LC_{50} was determined to be greater than 5.08 mg/L.

In an oral study, groups of 6 male and 6 female Sprague-Dawley rats received 0, 8, 40, 200, or 1000 mg/kg bw/d Hydroxy Tetramethylpiperidine Oxide via gavage for 28 d. Two additional recovery groups, consisting of 6 males and 6 females that were administered either the vehicle or the highest dose, were kept alive and observed for 14 d after treatment. Among sacrificed rats, the 1000 mg/kg group had decreased blood cell count and hemoglobin, increased spleen and liver weights, and blackened spleen was observed. A dose-dependent increase in congestion and hemosiderin-laden cells in the spleen and hepatocyte swelling was observed in the 200 mg/kg females, and both sexes in the 1000 mg/kg group. The NOAEL was determined to be 40 mg/kg bw/d. In another 28-d oral toxicity study, groups of 5 male and 5 female Sprague-Dawley rats received up to 1000 mg/kg bw of Tris(Tetramethylhydroxypiperidinol) Citrate via gavage. Two additional groups of 5 males and 5 females were dosed with 0 or 1000 mg/kg/d for 28 d, and then observed post-exposure for 14 d, serving as recovery groups. In the rats that were sacrificed, dose-dependent abnormalities, such as salivation and apparent blood around the facial area, neck and forelimbs, were identified in the males and females dosed with 500 and 1000 mg/kg bw/d; a statistically significant, slight decrease in red blood cell counts, hemoglobin, and hematocrit was seen in females. Spleen weights and congestion also increased, but these effects were reversible during the recovery period. The NOEL was determined to be 100 mg/kg bw/d.

In a 90-d dermal toxicity study, groups of 10 male and 10 female Wistar Han rats were exposed to an open application of up to 500 mg/kg bw/d, 97.3% pure, Tris(Tetramethylhydroxypiperidinol) Citrate. An additional two groups of 5 males and 5 females received open applications of 0 or 500 mg/kg bw/d of the test substance for 13 wk, and were observed for 4 wk post-

dosing as recovery animals; no premature deaths occurred. Scabs were noted at the application site during the treatment; aberrations in glucose, urea, white blood cell count, and potassium concentration were also observed in animals in the 50 and 500 mg/kg groups. The effect on glucose and urea was reversible; however, the effects on white blood cell count and potassium concentrations persisted. Based on the results of this study, the NOAEL was determined to be 150 mg/kg bw/d.

In a developmental toxicity study, groups of 22 female Wistar rats were mated, and dosed with up to 400 mg/kg bw/d of 98.4% Hydroxy Tetramethylpiperidine Oxide, via gavage, from day 6 to 21 of gestation. Statistically significant increases in hemoglobin, red blood cell, and reticulocyte count, accompanied by relative increases in spleen weights, aspartate, and alanine aminotransferase activity were observed in the 400 mg/kg dams. In the absence of a dose-response relationship, kidney dilation in pups from the 400 mg/kg litters was not considered toxicologically significant. The maternal NOAEL was determined to be 125 mg/kg/d, while the fetal NOAEL was determined to be 400 mg/kg/d.

Hydroxy Tetramethylpiperidine Oxide was weakly mutagenic in a bacterial reverse mutation assay, tested at up to 5000 µg/plate. Tris(Tetramethylhydroxypiperidinol) Citrate was not mutagenic in the Ames test, or in a chromosomal aberration assay using CHO cells, when tested at doses up to 5000 µg/plate. In micronucleus assays performed with mice, Hydroxy Tetramethylpiperidine Oxide (1200 mg/kg bw via gavage) and Tris(Tetramethylhydroxypiperidinol) Citrate (up to 200 mg/kg bw, administered intravenously) were not clastogenic.

Hydroxy Tetramethylpiperidine Oxide, at a dose of 0.5 g, did not cause dermal irritation when applied semi-occlusively to Klein Weisse rabbits for 4 h, or sensitization, when tested at the same dose in a Buehler test, using Pirbright Dunkin-Hartley guinea pigs. Tris(Tetramethylhydroxypiperidinol) Citrate, at a dose of 0.5 g, was considered non-irritating to the skin of 6 New Zealand White rabbits following semi-occlusive application to a 1 in^2 patch of shaved skin for 4 h. Undiluted Tris(Tetramethylhydroxypiperidinol) Citrate was not considered a sensitizer in a guinea pig maximization test. In clinical testing with 104 subjects, Tris(Tetramethylhydroxypiperidinol) Citrate was not a sensitizer.

Hydroxy Tetramethylpiperidine Oxide caused irreversible eye damage when instilled in the eyes of rabbits, at an undiluted dose of 0.1 g. Tris(Tetramethylhydroxypiperidinol) Citrate was considered non-irritating to 3 New Zealand White rabbit eyes. The mean irritation score was 0.78 (maximum score of 3), and irritation was fully reversible between 72 h and 10 d.

DISCUSSION

Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate are structurally related as piperidine nitroxides. Therefore, these cosmetic ingredients have been reviewed together in this assessment. Data for a few toxicological endpoints were either not available, or minimal, for the ingredient Tris(Tetramethylhydroxypiperidinol) Citrate. The Panel considered that Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate are essentially the same compound, in oxide and citrate salt forms, respectively. Therefore, the Panel felt that data on Hydroxy Tetramethylpiperidine Oxide could be used to substantiate the safety of both ingredients.

Although Tris(Tetramethylhydroxypiperidinol) Citrate is reported to function as a light stabilizer, the Panel discussed that its chemical structure does not have a chromophore and that it is known to act as a free radical scavenger. Hence, it would not be expected to pose phototoxicity concerns.

Initial concerns about the lack of carcinogenicity data were mitigated by sufficient data supporting a lack of genotoxic potential. Additionally, although the Panel noted very limited information on methods of manufacture and impurities for these ingredients, the description for a general synthesis of Hydroxy Tetramethylpiperidine Oxide and the high purity indicated for Tris(Tetramethylhydroxypiperidinol) Citrate (93.64- 97.3%), in conjunction with the lack of adverse effects in a 90-d dermal toxicity study, in which the NOAEL was 150 mg/kg bw/d, mitigated this concern. The safe dermal toxicity profile demonstrated in this report, in addition to a log K_{ow} value of -0.29, indicating minimal dermal penetration, reassured the Panel of safety.

Tris(Tetramethylhydroxypiperidinol) Citrate is reported to be used in products that could possibly be inhaled. For example, this ingredient is used in colognes and toilet waters at concentrations up to 0.05%. Little inhalation toxicity data (i.e., acute studies rats) were available; no adverse effects were noted. The Panel noted that in aerosol products, 95% – 99% 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 and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

TABLES

Table 1. Chemical Properties

Property	Value	Reference
Hydroxy Tetramethylpiperidine Oxide		
Physical Form (@ 20 °C and 1013 hPa)	Solid, orange flakes	3
Formula Weight (g/mol)	172.24	15
Topological Polar Surface Area (Å^2)	24.5 (calculated)	15
Density/Specific Gravity (g/cm^3 @ 20 °C)	1.127	
Vapor pressure (Pa @ 20 °C)	0.025	3
Melting Point (°C)	70 °C	3
Partition coefficient (@ 25 °C) log K_{ow}	0.56 (estimated, QSAR)	3
Dissociation constant (pKa @ 20 °C)	5.07	3
Surface tension (mg/l, in 1.0 g/l distilled water, @ 20 °C)	65.3	3
Water solubility (g/l @ 20 °C)	629.3	3
Tris(Tetramethylhydroxypiperidinol) Citrate		
Physical Form (@ 20 °C & 1013 hPa)	Solid	4
Formula Weight (g/mol)	711.9	16
Topological Polar Surface Area (Å^2)	263 (calculated)	16
Density/Specific Gravity (g/ml @ 24 ºC)	1.190	4
Vapor pressure (Pa @ 20ºC)	< 0.6	4
Melting Point (ºC)	59.17 - 64.26	4
Boiling Point (ºC)	Decomposed before boiling under nitrogen at atmospheric pressure	4
Partition coefficient (@ 20 °C & pH = 4) log K_{ow}	-0.29	4
Water Solubility (g/l @ 20.5 ºC)	> 500	4

Table 2. Frequency and concentration of use

	# of Uses[6] (2021)	Max Conc of Use (%)[7] (2020)	# of Uses[6] (2021)	Max Conc of Use (%)[8] (2018)
	Hydroxy Tetramethylpiperidine Oxide		**Tris(Tetramethylhydroxypiperidinol) Citrate**	
Totals*	**NR**	**0.005-0.019**	**125**	**0.0001-0.05**
Duration of Use				
Leave-On	*NR*	*0.005-0.019*	*111*	*0.0001-0.05*
Rinse-Off	*NR*	*NR*	*8*	*0.005-0.05*
Diluted for (Bath) Use	*NR*	*NR*	*6*	*NR*
Exposure Type				
Eye Area	NR	NR	3	0.005
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	48; 49[a]; 8[b]	0.0001-0.05; 0.0001-0.01[a]
Incidental Inhalation-Powder	NR	NR	8[b]	0.005-0.01[c]
Dermal Contact	NR	NR	122	0.0001-0.05
Deodorant (underarm)	NR	NR	NR	Not spray: 0.01
Hair - Non-Coloring	NR	NR	2	0.0001-0.01
Hair-Coloring	NR	NR	1	0.005
Nail	NR	0.005-0.019	NR	NR
Mucous Membrane	NR	NR	11	0.01-0.05
Baby Products	NR	NR	NR	NR

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

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

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

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

NR – not reported

Table 3. Acute toxicity studies

Ingredient	Animals	No./ Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
DERMAL						
Hydroxy Tetramethyl-piperidine Oxide	Sprague-Dawley rats	5/sex	water	OECD TG 402. Animals were dosed with 2000 mg/kg bw Hydroxy Tetramethylpiperidine Oxide, in water, via an occluded, 5x6 cm dressing for 24 h.	LD_{50} > 2000 mg/kg bw	[3]
Tris(Tetramethyl-hydroxypiperidinol) Citrate, 93.64%	New Zealand white rabbits	5/sex	Deionized water	OECD TG 402. Limit test involved applying test substance, neat, to 10% of the body surface area. An occlusive application of the substance in deionized water (1 mL of deionized water/g of test substance) at a dose of 2000 mg/kg bw, or 2136 mg/kg bw, was made for 24 h. The rabbits were observed for mortality and clinical abnormalities 14 d before euthanization.	No mortality or significant pathology observed. LD_{50} > 2136 mg/kg bw	[4]
ORAL						
Hydroxy Tetramethyl-piperidine Oxide	Tif/RAIf rats	5/sex	Distilled water	OECD TG 401. Animals received doses of 500, 1000, 2000 or 5000 mg/kg bw, via gavage. There were no controls in the study; the animals were observed for 14 d.	No mortality occurred in the 500 mg/kg group. Three males and 1 female died in the 1000 mg/kg group, while all males and females died in the 2000 mg/kg and 5000 mg/kg groups. LD_{50} values: 953 mg/kg bw (males) 1155 mg/kg bw (females) 1053 mg/kg bw (combined)	[3]
Tris(Tetramethyl-hydroxypiperidinol) Citrate	Sprague-Dawley rats	5/sex	Deionized water	OECD TG 401. Male rats received doses of 1068, 2136, 2670, and 3204 mg/kg bw, while female rats received doses of 534, 1068, 1602, or 2136 mg/kg bw, via gavage. There were no controls in this study. Animals were observed for mortality or clinical abnormalities for 14 d after exposure.	Mortality occurred in 3 male and 2 female rats given the highest dose. These animals exhibited abnormal digestive and pulmonary pathology. LD_{50} values: 2495 mg/kg bw (male) 1068 -1602 mg/kg bw (female) 1758 mg/kg bw (combined)	[4]
INHALATION						
Tris(Tetramethyl-hydroxypiperidinol) Citrate, 94.8%	Sprague-Dawley rats	5/sex	3.8% water, and 0.6% other	OECD TG 403. Animals were exposed nose-only for 4 h to a fine white powder, composed of the test substance which was aerosolized in a gravimetric chamber at a concentration of 5.08 mg/l. The estimated MMAD was 3.8 µm. The animals were observed for mortality and signs of gross toxicity for 14 d after exposure, and then necropsied.	No mortality or gross abnormalities occurred. LC_{50} > 5.08 mg/l	[4]

Table 4. Genotoxicity studies

Test Article	Concentration/ Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Hydroxy Tetramethylpiperidine Oxide*	Up to 5000 µg/plate; with or without metabolic activation	Water DMSO	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537	Bacterial reverse mutation assay, in accordance with OECD TG 471	Weakly mutagenic. The test substance was weakly mutagenic (generally, test concentration not specified) in *S. typhimurium* strains TA 100 and 1537, including base-pair and frameshift mutations, in the presence of metabolic activation.	[3]
Tris(Tetramethylhydroxypiperidinol) Citrate, 93.64%	100, 333, 1000, 3330, or 5000 µg/plate; with or without metabolic activation	DMSO	*S. typhimurium* strains TA 1535, TA 1537, TA 98, TA 100 and *Escherichia coli* WP2 uvr A	Ames, mammalian-microsome reverse mutation assay, in accordance with OECD TG 471	Not genotoxic	[4]
Tris(Tetramethylhydroxypiperidinol) Citrate*	Up to 5000 µg/ml; with or without metabolic activation	Water	Chinese hamster ovary cell line (CHO)	Chromosomal aberration test, in accordance with OECD TG 473	Not genotoxic Weak increase in cells with aberrations was observed at the 5000 µg/ml dose. No significant increase in cells with chromosomal abnormalities, polyploidy, or endoreduplication was observed.	[4]
IN VIVO						
Hydroxy Tetramethylpiperidine Oxide*	1200 mg/kg bw, via gavage	Saline; cyclophosphamide	5 male and 5 female NMRI mice	Micronucleus assay, in accordance with OECD TG 474	Not genotoxic Clinical symptoms such as hunched posture, sedation, piloerection, and death were observed. Induction of micronuclei did not occur.	[3]
Tris(Tetramethylhydroxypiperidinol) Citrate, 93.64%	50, 100, or 200 mg/kg bw, intravenous injection	Water; cyclophosphamide (positive control, given orally)	Groups of 6 male CD-1 mice	Micronucleus assay, in accordance with OECD TG 474. Five animals from the 50 and 100 mg/kg groups and 5 animals from the positive control group were euthanized about 24 h after dosing for bone marrow extraction. Five animals from the 200 mg/kg and 5 from the vehicle group were euthanized about 24 and 48 h after dosing for bone marrow extraction.	Non-clastogenic. Clinical toxicity was observed in the 200 mg/kg animals and 2 animals from this group died. The test item did not induce a statistically significant increase in the frequency of micronucleated polychromatic erythrocytes.	[4]

*Composition not specified
DMSO – dimethyl sulfoxide

Table 5. Dermal irritation and sensitization studies

Test Article	Concentration/ Dose (Vehicle)	Test Population	Procedure	Results	Reference
ANIMAL					
Hydroxy Tetramethylpiperidine Oxide*	0.5 g (water)	3 male Klein Weisse Russen rabbits	Acute dermal irritation test, in accordance with OECD TG 404. The test article, in 0.5 cm^3 water, was applied to the shaved backs of the animals in a 6 cm^2, semi-occlusive dressing, for 4 h. The test sites were washed with water after exposure and were observed for up to 72 h.	Non-irritating	[3]
Hydroxy Tetramethylpiperidine Oxide*	0.5 g (at 50% w/w, in petrolatum)	29 Pirbright Dunkin-Hartley guinea pigs	Buehler test, in accordance with OECD TG 406. Three, 6-h, occluded induction applications were made to the shaved backs of the animals on day 0, 7, and 14. The challenge application was made, in the same manner, on day 28, and the test site was evaluated at 30 and 54 h after challenge.	Non-sensitizing	[3]
Tris(Tetramethylhydroxypiperidinol) Citrate; 93.64%	0.5 g (water)	3 male and 3 female New Zealand white rabbits	In accordance with OECD TG 404. The test article was applied for 4 h to 1 in^2 of shaved skin using a semi-occlusive patch. Test sites were washed with deionized water after exposure, dried with gauze, and observed for up to 7 d.	Non-irritating Mean erythema score of 1 (maximum score of 4) and mean edema score of 0 were reported; erythema was completely reversible by day 7. According to EC Regulation No. 1272/2008 criteria, was considered non-irritating.	[4]
Tris(Tetramethylhydroxypiperidinol) Citrate*	5.0% w/v (in deionized water) for intradermal injection; tested undiluted for induction and challenge	10 male and 10 female Hartley albino guinea pigs	Guinea pig maximization test, in accordance with OECD TG 406. Intradermal injections of the test substance in deionized water were injected into the animals, along with FCA, and the test article in FCA. The control group (5 male and 5 female guinea pigs) received the same injections, but without the test article. On day 6, 0.5 ml of 10% w/w sodium lauryl sulfate in petrolatum was spread over the intradermal injection sites of all animals. On day 7, any residual sodium lauryl sulfate was removed, and patches with undiluted test article, or water, were applied to the test animals for 48 h. Challenge applications were made on day 20 using Hilltop chambers, and re-challenge applications were made 8 d later in test and control groups.	Non-sensitizing Group mean dermal scores were noted to be similar in test animals compared with the challenge control animals.	[4]
HUMAN					
Tris(Tetramethylhydroxypiperidinol) Citrate*	0.1% or 0.5%; 0.2 ml (in water)	104 subjects	Modified Draize test. Nine occlusive induction applications were made for 24 h with the test article, over 3 wk. The control was water or 0.1% sodium lauryl sulfate. Test sites were wiped with water after each testing phase. After a rest period of 10 -17 d, a previously unexposed site was challenged with the test substance for 24 h.	Non-sensitizing Three adverse events were reported during the course of the study, but they were not related to the exposure to the test substance. The test substance did not appear to cause sensitization during the 3-wk induction period or during the challenge phase.	[4]

*Composition not specified
DCNB – 1,2-dichloro-4-nitrobenzene
FCA- Freund's Complete Adjuvant
NR -not reported

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2021 FDA Frequency of Use Data for Tris(Tetramethylhydroxypiperidinol) Citrate
Total: 125

Category	CAS_number	Ingredient_name	Cpis_count
02A-Bath Oils, Tablets, and Salts	999001431	Tris (tetramethylhydroxypiperidinol) citrate	2
02D -Other Bath Preparations	999001431	Tris (tetramethylhydroxypiperidinol) citrate	4
03D- Eye Lotion	999001431	Tris (tetramethylhydroxypiperidinol) citrate	2
03G - Other Eye Makeup Preparations	999001431	Tris (tetramethylhydroxypiperidinol) citrate	1
04A -Cologne and Toilet waters	999001431	Tris (tetramethylhydroxypiperidinol) citrate	23
04B- Perfumes	999001431	Tris (tetramethylhydroxypiperidinol) citrate	24
04E - Other Fragrance Preparation	999001431	Tris (tetramethylhydroxypiperidinol) citrate	1
05A - Hair Conditioner	999001431	Tris (tetramethylhydroxypiperidinol) citrate	1
05F - Shampoos (non-coloring)	999001431	Tris (tetramethylhydroxypiperidinol) citrate	1
06C - Hair Rinses (coloring)	999001431	Tris (tetramethylhydroxypiperidinol) citrate	1
10A - Bath Soaps and Detergents	999001431	Tris (tetramethylhydroxypiperidinol) citrate	4
10E - Other Personal Cleanliness Products	999001431	Tris (tetramethylhydroxypiperidinol) citrate	1
12C - Face and Neck (exc shave)	999001431	Tris (tetramethylhydroxypiperidinol) citrate	5
12D - Body and Hand (exc shave)	999001431	Tris (tetramethylhydroxypiperidinol) citrate	3
12F - Moisturizing	999001431	Tris (tetramethylhydroxypiperidinol) citrate	46
12G - Night	999001431	Tris (tetramethylhydroxypiperidinol) citrate	2
12J - Other Skin Care Preps	999001431	Tris (tetramethylhydroxypiperidinol) citrate	3
13C - Other Suntan Preparations	999001431	Tris (tetramethylhydroxypiperidinol) citrate	1

Concentration of Use by FDA Product Category - Hydroxy Tetramethylpiperidine Oxide

Product Category	Maximum Concentration of Use
Basecoats and undercoats (manicuring preparations)	0.019%
Nail polish and enamel	0.005%

Information collected in 2020

Table prepared: October 7, 2020

Corrected: 12.5% basecoats and undercoats concentration to 0.019%

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: January 11, 2021

SUBJECT: Tentative Report: Safety Assessment of Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate as Used in Cosmetics (release date December 16, 2020)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate as Used in Cosmetics.

Dermal Irritation and Sensitization – The 4-hour study of Tris(Tetramethylhydroxypiperidinol) Citrate in rabbits is an irritation study not a sensitization study. Rather than stating “deemed non-sensitizing” it should state “deemed non-irritating”. This would be consistent with the information presented in Table 5.

Dermal Irritation and Sensitization; Summary; Table 5 – Please check the details of the guinea pig maximization test of Tris(Tetramethylhydroxypiperidinol) Citrate. Reference 4 states that the intradermal injection concentration used was 5% and that they dosed the guinea pigs with 100% for the topical induction, challenge and rechallenge. The CIR report only states the 5% concentration.

Summary – Please indicate that the highest use concentration of Hydroxy Tetramethylpiperdine Oxide was reported in basecoats and undercoats (rather than “other manicuring preparations”).

Please add the word “study” after “In an acute inhalation toxicity”

The Buehler test in guinea pigs is a sensitization test, while the 4-hour study in rabbits is an irritation test not a sensitization test.

Discussion – It would be helpful to also mention the acute inhalation study in the Discussion.