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

Status: Draft Tentative Report for Panel Review
Release Date: November 13, 2020
Panel Meeting Date: December 7-8, 2020

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.



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

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

Date: November 13, 2020

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

Enclosed is the Draft Tentative Report on the Safety Assessment of Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate as Used in Cosmetics (identified as *tricit122020rep* in the pdf). This is the second time the Panel is seeing a safety assessment of these cosmetic ingredients. At the June 2020 Panel meeting, a draft report was presented to the Panel. Upon review, the Panel issued an Insufficient Data Announcement for method of manufacture and impurities, for which no data have been received.

The first time the Panel saw this assessment it was a single-ingredient report (only Tris(Tetramethylhydroxypiperidinol) Citrate). The Council proposed the addition of two chemically-similar substances, Hydroxy Tetramethylpiperidine Oxide and tetramethylpiperidine nitroxide, which the Panel agreed upon. The first proposed substance is a cosmetic ingredient, and has thus been incorporated as an additional ingredient, while the second substance has been added as read-across. The newly added data have been added to the report, and are highlighted in yellow. These data include 2020 concentration of use data received for Hydroxy Tetramethylpiperidine Oxide (*tricit122020data*).

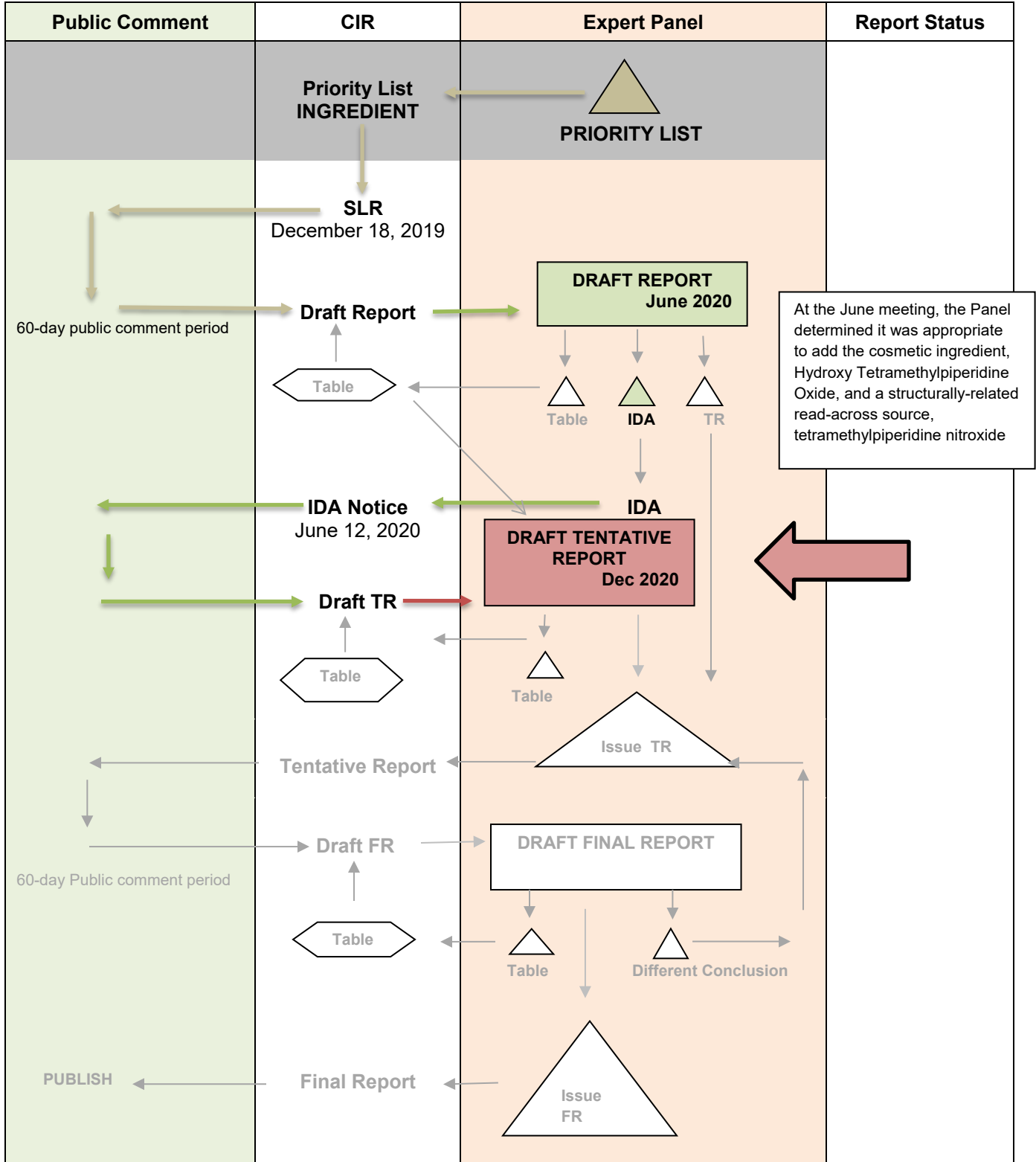
Additional comments from Council were not received. Included in this package for your review are a search strategy (*tricit122020strat*), report history (*tricit122020hist*), flowchart (*tricit122020flow*), transcripts from the previous meeting (*tricit122020min*), data profile (*tricit122020prof*), and 2020 FDA VCRP data (*tricit122020fda*).

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

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate

MEETING December 2020



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
- Inhalation toxicity data

No unpublished data were received from Council or the industry.

March 2020

Council proposed the addition of data for 2 substances -- Hydroxy Tetramethylpiperidine Oxide, a cosmetic ingredient (CAS No. 2226-96-2), and another structurally related non-cosmetic ingredient, tetramethylpiperidine nitroxide (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 adding data for the two proposed substances. Hydroxy Tetramethylpiperidine Oxide was added as an additional cosmetic ingredient, while tetramethylpiperidine nitroxide was added as a read-across source.

- October 8, 2020: Concentration of use data were received from Council for Hydroxy Tetramethylpiperidine Oxide

December 2020

A Draft Tentative Report is being presented for Panel review.

Tris(Tetramethylhydroxypiperidinol) Citrate Data Profile* – December 7-8th, 2020 – Writer, Preethi Raj

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization			Phototoxicity	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		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		
<i>Read across sources</i>																													
tetramethylpiperidine nitroxide				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
2,2,6,6-tetramethyl-4-piperidine-N-oxide	2564-83-2	✓	0/0	NR	NR	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 PubMed and Toxnet - total # of useful hits / # total number of hits]*

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

Hydroxy tetramethylpiperidine oxide OR 2226-96-2 AND dermal irritation – 0/3

Hydroxy tetramethylpiperidine oxide OR 2226-96-2 AND dermal sensitization – 0/5

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
2,2,6,6-tetramethyl-4-piperidine-N-oxide OR 2564-83-2 AND dermal irritation - 0/184
2,2,6,6-tetramethyl-4-piperidine-N-oxide OR 2564-83-2 AND dermal sensitization – 0/127

General search:

hydroxy tetramethylpiperidine oxide and dermal irritation – 0/399
hydroxy tetramethylpiperidine oxide and dermal sensitization - 0/13,700
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
2,2,6,6-tetramethyl-4-piperidine-N-oxide and dermal irritation – 0/19,800
2,2,6,6-tetramethyl-4-piperidine-N-oxide and dermal sensitization - 0/30,200

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/fcnavigation.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.

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

Status: Draft Tentative Report for Panel Review
Release Date: November 13, 2020
Panel Meeting Date: December 7-8, 2020

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.

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 a light stabilizer and an antioxidant, respectively. The Panel reviewed relevant data relating to the safety of these ingredients, and one structurally similar read-across source, in cosmetic formulations and concluded...[to be determined].

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

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.³⁻⁵ At the June 2020 Expert Panel meeting, the Personal Care Products Council (Council) proposed the addition of available data related to the cosmetic ingredient, Hydroxy Tetramethylpiperidine Oxide, and another chemical substance, tetramethylpiperidine nitroxide, as a read-across source. The Panel noted the analogous structural features and radical scavenging activity of Tris(Tetramethylhydroxypiperidinol) Citrate, Hydroxy Tetramethylpiperidine Oxide, and tetramethylpiperidine nitroxide, and agreed to these additions. Data has therefore been incorporated for Hydroxy Tetramethylpiperidine Oxide, as an additional cosmetic ingredient, and for tetramethylpiperidine nitroxide, as a read across substance, herein. 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(Tetramethylhydroxypiperidinol) Citrate (CAS No. 220410-74-2) is a salt; these piperidine nitroxides conform to the structures shown in Figures 1 and 2.¹

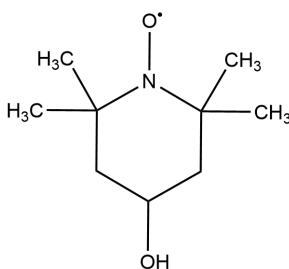


Figure 1. Hydroxy Tetramethylpiperidine Oxide

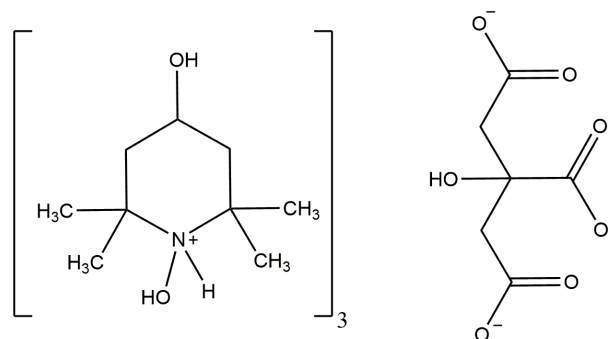


Figure 2. Tris(Tetramethylhydroxypiperidinol) Citrate

The chemical substance, tetramethylpiperidine nitroxide (CAS No. 2564-83-2), is considered a suitable read-across source for these ingredients; justification for the use of tetramethylpiperidine nitroxide as a read-across source is provided in Table 1.

Chemical Properties

Hydroxy Tetramethylpiperidine Oxide has a formula weight of 172.24 g/mol and a calculated log P_{ow} of 0.56,⁴ while Tris(Tetramethylhydroxypiperidinol) Citrate has a formula weight of 711.9 g/mol and a log P_{ow} of -0.29;³ both are soluble in water. The chemical properties of these cosmetic ingredients, and the read-across source, are further outlined in Table 2.

Method of Manufacture

A general synthesis mechanism for Hydroxy Tetramethylpiperidine Oxide involves derivation from triacetoneamine.⁶ 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;⁷ 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 12.5% in basecoats and undercoats.⁸ According to 2020 VCRP data, Tris(Tetramethylhydroxypiperidinol) Citrate is reported to be used in 388 cosmetic formulations, most of which are leave-on formulations (335 uses; Table 3).⁷ 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.⁹

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%. According to VCRP data, Tris(Tetramethylhydroxypiperidinol) Citrate is used in a baby product formulation; however, concentration of use data were not reported for any baby products.

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.^{10,11} 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.^{12,13}

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.¹⁴

Non-Cosmetic

Data for the non-cosmetic use of Tris(Tetramethylhydroxypiperidinol) Citrate was not found. A well-known use for the read-across source, tetramethylpiperidine nitroxide, is as an oxidation catalyst, in the industrial conversion of alcohols into aldehydes, ketones, and carboxylic acids, as well as in the oxidation of sulfides and organometallic compounds.⁶ Clinically, Hydroxy Tetramethylpiperidine Oxide and tetramethylpiperidine nitroxide have been noted for their potential as nitroxides to provide protection against radiation and oxidative stresses, both in vitro and in vivo.¹⁵

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 4.

The dermal LD₅₀ of Hydroxy Tetramethylpiperidine Oxide was determined to be > 2000 mg/kg bw in male and female Sprague-Dawley rats.⁴ The dermal LD₅₀ of Tris(Tetramethylhydroxypiperidinol) Citrate was determined to be > 2136 mg/kg bw in male and female New Zealand white rabbits.³ The dermal LD₅₀ of tetramethylpiperidine nitroxide was determined to be < 2000 mg/kg in New Zealand white rabbits after an 24 – h, occlusive application of 2000 mg/kg was made; 3 out of 4 of the tested animals died within 21 h, exhibiting discoloration and pathological changes in the liver, lungs, and at the site of testing.⁵

The oral LD₅₀ 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.⁴ In an acute oral toxicity study of Tris(Tetramethylhydroxypiperidinol) Citrate, the LD₅₀ 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.³

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.³ The LC₅₀ 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.⁴ 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.³ 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

The dermal toxicity of Tris(Tetramethylhydroxypiperidinol) Citrate (97.3% pure) was evaluated in a 90-d study in rats, according to OECD TG 411.³ 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 cm² in males and 30 – 35 cm² 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, embryonic, and fetal development.⁴ Dams were mated overnight and 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 5.

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.⁴ 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, tested in an Ames test, either in the presence or absence of metabolic activation.³ In a chromosomal aberration test with Tris(Tetramethylhydroxypiperidinol) Citrate 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.³ Cytotoxic effects and a statistically significant increase in the number of revertants were observed when *S. typhimurium* strain TA 100 was tested with up to 30.0 µmol tetramethylpiperidine nitroxide.⁵

In vivo, several micronucleus tests were performed in mice. No genotoxicity was observed with Hydroxy Tetramethylpiperidine Oxide, at 1200 mg/kg bw (by gavage),⁴ Tris(Tetramethylhydroxypiperidinol) Citrate, at up to 200 mg/kg (administered intravenously),³ or tetramethylpiperidine nitroxide, at 1200 mg/kg bw (by gavage).⁵

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 6.

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.⁴ Tris(Tetramethylhydroxypiperidinol) Citrate was deemed non-sensitizing 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, when tested at 5.0% w/v in male and female Hartley albino guinea pigs in a maximization test.³ Dermal irritation was observed when 3 male and 3 female New Zealand white rabbits were exposed to an occluded application of 0.5 g tetramethylpiperidine nitroxide, the read-across source, for 4 h; histological examination of animals with severe reactions showed signs of necrosis.⁵ An undisclosed concentration of tetramethylpiperidine nitroxide was deemed non-sensitizing in a guinea pig maximization test.⁵

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.³

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 405.⁴ 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 405.³ 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.

Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate (tetramethylpiperidine nitroxide, a read-across source)

The ocular irritation potential of the read-across source, tetramethylpiperidine nitroxide, was evaluated in the eyes of 3 male and 3 female New Zealand white rabbits, in a manner similar to OECD TG 405.⁵ An undiluted dose of 0.1 g tetramethylpiperidine nitroxide was instilled in the conjunctival sac of one eye, while the other eye served as a control. The test article was not removed and the animals were observed for up to 21 d after treatment. The treated eyes were scored after 24, 48, and 72 h of exposure. While positive irritation scores for corneal opacity, iris, conjunctivae, and chemosis were observed and reversible, 3 animals with progressively worsening ocular symptoms were killed on day 7, as the observed effects were deemed irreversible. Due to trends in severity, longer time needed for reversibility, and the progressive deterioration in half of the study animals, the test material was deemed a Category 1 substance, causing serious and irreversible damage to the eye.

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 2020, VCRP data were not available for Hydroxy Tetramethylpiperidine Oxide; Tris(Tetramethylhydroxypiperidinol) Citrate was reported to be used in 388 formulations. According to Council survey data, Hydroxy Tetramethylpiperidine Oxide is reported to be used at a maximum concentration of 12.5% in manicuring preparations (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 LD₅₀ 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 LD₅₀ was determined to be > 2136 mg/kg bw. The dermal LD₅₀ of tetramethylpiperidine nitroxide in 4 New Zealand white rabbits was determined to be < 2000 mg/kg; 3 out of 4 of the tested animals died within 21 h of exposure.

In an acute oral toxicity study, 40 Tif/RAIf rats received 500, 1000, 2000, or 5000 mg/kg bw Hydroxy Tetramethylpiperidine Oxide, via gavage. Mortality occurred in 5 males and 6 females from the 1000 and 2000 mg/kg groups, and all animals in the 5000 mg/kg group. The oral LD₅₀ for both sexes (combined) was determined to be 1053 mg/kg bw. In an acute

oral toxicity study, 40 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, who received the highest dose, died prior to scheduled necropsy. The oral LD₅₀ for both sexes (combined) was determined to be 1758 mg/kg bw.

In an acute inhalation toxicity, 10 Sprague-Dawley rats were exposed to aerosolized 94.8% pure Tris(Tetramethylhydroxypiperidinol) Citrate (estimated MMAD 3.8 µm), at a concentration of 5.08 mg/L, nose-only, for 4 h. The acute inhalation LC₅₀ 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 rats 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, tested at concentrations up to 5000 µg/plate. A positive mutagenic response was observed for the read-across source, tetramethylpiperidine nitroxide, tested at up to 30 µmol/plate. In micronucleus assays performed with mice, up to 200 mg/kg bw, intravenously dosed, Tris(Tetramethylhydroxypiperidinol) Citrate, and Hydroxy Tetramethylpiperidine Oxide and tetramethylpiperidine nitroxide, dosed via gavage at 1200 mg/kg bw, 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 when tested at the same dose in a Buehler test, using Pirbright Dunkin-Hartley guinea pigs. Tris(Tetramethylhydroxypiperidinol) Citrate was considered non-sensitizing to the skin of 6 New Zealand White rabbits following semi-occlusive application to a 1 in² patch of shaved skin for 4 h. Tris(Tetramethylhydroxypiperidinol) Citrate was not considered a sensitizer in a guinea pig maximization test. A neat, occluded application of 0.5 g tetramethylpiperidine nitroxide, the read-across source, showed signs of dermal irritation, and necrosis, in New Zealand white rabbits. No sensitizing potential of tetramethylpiperidine nitroxide was observed in a guinea pig maximization test. In clinical testing with 104 subjects, Tris(Tetramethylhydroxypiperidinol) Citrate was not a sensitizer.

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. Both Hydroxy Tetramethylpiperidine Oxide and the read-across source, tetramethylpiperidine nitroxide, caused irreversible eye damage when instilled in the eyes of rabbits, at an undiluted dose of 0.1 g.

DRAFT DISCUSSION

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

Hydroxy Tetramethylpiperidine Oxide, Tris(Tetramethylhydroxypiperidinol) Citrate, and the read-across source, tetramethylpiperidine nitroxide, are structurally related as piperidine nitroxides; therefore, these chemicals are being 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 tetramethylpiperidine nitroxide has a similar chemical and toxicological profile to Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate, and felt that this read-across source could be utilized, as appropriate, to further support data for the 2 cosmetic ingredients. The potential effect of an absent hydroxyl group in tetramethylpiperidine nitroxide was briefly discussed, but was not considered of concern. Furthermore, the Panel deemed that this read-across source shares the chemical function of Tris(Tetramethylhydroxypiperidinol) Citrate, i.e., trapping and absorbing radicals. Although Tris(Tetramethylhydroxypiperidinol) Citrate is reported to function as a light stabilizer, the Panel discussed how its chemical structure does not have a chromophore and that it is known to act as a free radical scavenger; hence, it would not pose phototoxicity concerns.

The Panel considered the minimal likelihood for dermal absorption of these ingredients. Initial concerns about the lack of carcinogenicity data were mitigated by sufficient data supporting a lack of genotoxic potential. Furthermore, the Panel was reassured by data from a 90-d dermal exposure study in which Tris(Tetramethylhydroxypiperidinol) Citrate, was dosed at 500 mg/kg bw/d, a concentration much higher than the highest reported concentration of use, 0.05% in cologne and toilet waters, and bath soaps and detergents, and did not show significant toxicity. The safe dermal toxicity profile demonstrated in this study, in addition to no genotoxic concerns or structural alerts, and a log K_{ow} value of -0.29 reassured the Panel of minimal dermal penetration and safety.

The Panel discussed the issue of incidental inhalation exposure from fragrance preparations. The Council survey results indicate that Tris(Tetramethylhydroxypiperidinol) Citrate is being used in colognes, toilet waters, and other fragrance preparations at concentrations up to 0.05%. 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

To be determined.

TABLES**Table 1. Read across justification**

Targets Ingredients		Read-Across Source
Name	<i>Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate</i>	<i>tetramethylpiperidine nitroxide</i> ⁵
CAS No.	220410-74-2; 2226-96-2	2564-83-2
Structure	<p>The image shows three chemical structures. On the left is the structure of Hydroxy Tetramethylpiperidine Oxide, a piperidine ring with a hydroxyl group at the 4-position and four methyl groups at the 1, 2, 3, and 6 positions, with a positive charge on the nitrogen. In the middle is the structure of Tris(Tetramethylhydroxypiperidinol) Citrate, showing three of the hydroxy tetramethylpiperidine units coordinated to a central citrate molecule. On the right is the structure of tetramethylpiperidine nitroxide, a piperidine ring with four methyl groups and a nitroxide group at the 1-position.</p>	
read-across endpoints	←	<ul style="list-style-type: none"> • genotoxicity, in vitro and in vivo • dermal irritation and sensitization, animal • ocular irritation, animal
justification	Structurally similar piperidine oxides (the source is sans the 4-hydroxyl group), which also share the function of a radical scavenger and oxidation catalyst.	

Table 2. Chemical Properties

Property	Value	Reference
Hydroxy Tetramethylpiperidine Oxide		
Physical Form (@ 20 °C and 1013 hPa)	Solid, orange flakes	4
Formula Weight (g/mol)	172.24	16
Topological Polar Surface Area (Å ²)	24.5 (calculated)	16
Density/Specific Gravity (g/cm ³ @ 20 °C)	1.127	
Vapor pressure (Pa @ 20 °C)	0.025	4
Melting Point (°C)	70 °C	4
Partition coefficient (@ 25 °C) log K _{ow}	0.56 (calculated, QSAR)	4
Dissociation constant (pKa @ 20 °C)	5.07	4
Surface tension (mg/l, in 1.0 g/l distilled water, @ 20 °C)	65.3	4
Water solubility (g/l @ 20 °C)	629.3	4
Tris(Tetramethylhydroxypiperidinol) Citrate		
Physical Form (@ 20 °C & 1013 hPa)	Solid	3
Formula Weight (g/mol)	711.9	17
Topological Polar Surface Area (Å ²)	263 (calculated)	17
Density/Specific Gravity (g/ml @ 24 °C)	1.190	3
Vapor pressure (Pa @ 20°C)	< 0.6	3
Melting Point (°C)	59.17 - 64.26	3
Boiling Point (°C)	Decomposed before boiling under nitrogen at atmospheric pressure	3
Partition coefficient (@ 20 °C & pH = 4) log K _{ow}	-0.29	3
Water Solubility (g/l @ 20.5 °C)	> 500	3

Table 2. Chemical Properties

Property	Value	Reference
	tetramethylpiperidine nitroxide	
Physical Form (@ 20 °C and 1013 hPa)	Solid	5
Formula Weight (g/mol)	156.25	18
Topological Polar Surface Area (Å ²)	4.2 (calculated)	18
Density/Specific Gravity (g/cm ³ @ 25 °C)	0.898	5
Vapor pressure (hPa @ 20 °C)	0.4	5
Melting Point (°C)	36-40	
Partition coefficient (@ 25 °C & pH = 7.3-8.5) log K _{ow} (mean value)	2.5	5
Water solubility (g/l @ 20 °C)	11.6	5

Table 3. Frequency and concentration of use

	# of Uses ⁷ (2020)	Max Conc of Use (%) ⁸ (2020)	# of Uses ⁷ (2020)	Max Conc of Use (%) ⁹ (2018)
	Hydroxy Tetramethylpiperidine Oxide		Tris(Tetramethylhydroxypiperidinol) Citrate	
Totals*	NR	0.005-12.5	388	0.0001-0.05
Duration of Use				
<i>Leave-On</i>	NR	0.005-12.5	335	0.0001-0.05
<i>Rinse-Off</i>	NR	NR	44	0.005-0.05
<i>Diluted for (Bath) Use</i>	NR	NR	9	NR
Exposure Type				
Eye Area	NR	NR	5	0.005
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	154; 138 ^a ; 26 ^b	0.0001-0.05; 0.0001-0.01 ^a
Incidental Inhalation-Powder	NR	NR	26 ^b ; 1 ^c	0.005-0.01 ^c
Dermal Contact	NR	NR	372	0.0001-0.05
Deodorant (underarm)	NR	NR	2 ^a	Not spray: 0.01
Hair - Non-Coloring	NR	NR	15	0.0001-0.01
Hair-Coloring	NR	NR	1	0.005
Nail	NR	0.005-12.5	NR	NR
Mucous Membrane	NR	NR	31	0.01-0.05
Baby Products	NR	NR	1	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 4. 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	4
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	3
tetramethylpiperidine nitroxide	New Zealand white rabbits	2/sex		OECD TG 402. An undiluted, occlusive application of 2000 mg/kg tetramethylpiperidine nitroxide was made to an approximate 240 cm ² , clipped region of the back for 24 h. The test sites were rinsed with 0.9% sodium chloride and towel dried. The rabbits were observed for up to 14 d after patch removal.	LD ₅₀ < 2000 mg/kg bw 3 out of 4 animals died within 21 h of exposure. Animals which died exhibited red lungs and tracheal mucosa, pale liver with tan areas and/or reticulated capsular surface, fluid in the pleural cavity, fluid in the pericardium, and skin lesions, orange/brown discoloration and edema at the test site. No gross lesions, aside from the test site, were observed in the surviving rabbit.	5
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.	5 males and 6 females from the 1000 and 2000 mg/kg groups, and all animals in the 5000 mg/kg group died on day 1. LD ₅₀ values: 953 mg/kg bw (males) 1155 mg/kg bw (females) 1053 mg/kg bw (combined)	4
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)	3
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	3

Table 5. 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	<i>Salmonella typhimurium</i> 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 <i>S. typhimurium</i> strains TA 100 and 1537, including base-pair and frameshift mutations, in the presence of metabolic activation.	4
Tris(Tetramethylhydroxypiperidinol) Citrate, 93.64%	100, 333, 1000, 3330, or 5000 µg/plate; with or without metabolic activation	DMSO	<i>S. typhimurium</i> strains TA 1535, TA 1537, TA 98, TA 100 and <i>Escherichia coli</i> WP2 uvr A	Ames, mammalian-microsome reverse mutation assay, in accordance with OECD TG 471	Not genotoxic	3
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.	3
tetramethylpiperidine nitroxide*	0.06, 0.6, 1.5, 3, 6, 15, or 30 µmol/plate	DMSO	<i>S. typhimurium</i> strain TA 100	Bacterial reverse mutation assay, in accordance with OECD TG 471	Positive for mutagenicity. A cytotoxic effect was observed at the 30 µmol/plate dose. A weak but statistically significant increase in the number of revertants (180 to 210 revertants/plate) was observed between the 6 and 15 µmol dose.	5
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.	4
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.	3
tetramethylpiperidine nitroxide*	1200 mg/kg bw, via gavage	Saline; cyclophosphamide	5 male and 5 female NMRI mice	Micronucleus assay. Post-exposure observation at 24 and 48 h.	Not genotoxic Sedation in males, staggering gait, hunched posture, convulsions, and death in 2 males was observed. No statistically or biologically significant increase in micronucleated polychromatic erythrocytes occurred.	5

*Composition not specified
DMSO – dimethyl sulfoxide

Table 6. 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	4
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	4
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.	3
Tris(Tetramethylhydroxypiperidinol) Citrate*	5.0% w/v; (deionized water)	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 rechallenge 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.	3
tetramethylpiperidine nitroxide*	0.5 g (neat)	3 male and 3 female New Zealand white rabbits	Acute dermal irritation test, in accordance with OECD TG 404. The undiluted test article was applied to the shaved backs of the animals in a 2.5 x 2.3 cm, occluded dressing for 4 h. The test sites were rinsed with 0.9% saline after exposure and were observed for 21 d.	Positive for irritation Brown areas were seen in the test sites for all tested rabbits within 30-60 min of patch removal, and persisted through the 72-h scoring interval. Necrosis of the epidermis and dermis was evident upon histological examination of 2 rabbits displaying severe dermal irritation. Eschar formations persisted till up to day 14 in the remaining animals.	5
tetramethylpiperidine nitroxide*	NR (petrolatum) DCNB, 0.01% (positive control)	10 guinea pigs/group	Guinea pig skin maximization test, in accordance with OECD TG 406. After the intradermal injections of FCA, the animals were induced with a slightly irritating, single, occluded application of the test substance, in petrolatum, for 48 h. On day 24, the test substance was applied, in petrolatum, at a non-irritating concentration to a shaved back, under occlusion, for 24 h. The skin was cleaned, and inspected 24, 48, and 72 h after patch removal.	Non-sensitizing	5

Table 6. Dermal irritation and sensitization studies

Test Article	Concentration/ Dose (Vehicle)	Test Population	Procedure	Results	Reference
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.	3

*Composition not specified

DCNB – 1,2-dichloro-4-nitrobenzene

FCA- Freund's Complete Adjuvant

NR -not reported

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2020 FDA Frequency of Use Data for Tris(Tetramethylhydroxypiperidinol) Citrate**Total: 388**

CATEGORY	CAS_ NUMBER	MAINTERM	CPIS_ COUNT
01B - Baby Lotions, Oils, Powders, and Creams	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	1
02A- Bath Oils, Tablets, and Salts	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	2
02B - Bubble Baths	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	3
02D - Other Bath Preparations	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	4
03D - Eye Lotion	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	5
04A - Cologne and Toilet waters	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	76
04B - Perfumes	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	65
04E - Other Fragrance Preparation	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	13
05A - Hair Conditioner	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	4
05F - Shampoos (non-coloring)	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	9
05I - Other Hair Preparations	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	2
06C - Hair Rinses (coloring)	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	1
10A - Bath Soaps and Detergents	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	19
10B - Deodorants (underarm)	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	2
10E - Other Personal Cleanliness Products	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	5
11A - Aftershave Lotion	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	4
11F - Shaving Soap	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	3

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12A - Cleansing	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	2
12C - Face and Neck (exc shave)	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	12
12D - Body and Hand (exc shave)	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	14
12F - Moisturizing	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	135
12G - Night	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	2
12H - Paste Masks (mud packs)	999001431	TRIS (TETRAMETHYLHYDROXYPIPERIDINOL) CITRATE	1
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)	12.5%
Nail polish and enamel	0.005%

Information collected in 2020
Table prepared: October 7, 2020