Safety Assessment of Tris(Tetramethylhydroxypiperidinol) Citrate as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	May 15, 2020
Panel Meeting Date:	June 8-9, 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.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.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. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR.

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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: May 15, 2020

Subject: Draft Report on Tris(Tetramethylhydroxypiperidinol) Citrate as Used in Cosmetics

Enclosed is the draft report of Tris(Tetramethylhydroxypiperidinol) Citrate (identified as *tricit062020rep* in the pdf). This is the first time the Panel is seeing a safety assessment of this cosmetic ingredient. A Scientific Literature Review (SLR) was announced on December 18, 2019.

Comments on the SLR (*tricit062020pcpc*) that were received from the Council have been addressed. Also included in this package for your review are a literature search strategy (*tricit062020strat*), ingredient data profile (*tricit062020prof*), ingredient history (*tricit062020hist*), 2020 FDA VCRP data (*tricit062020FDA*), and 2018 concentration of use data (*tricit062020data)*.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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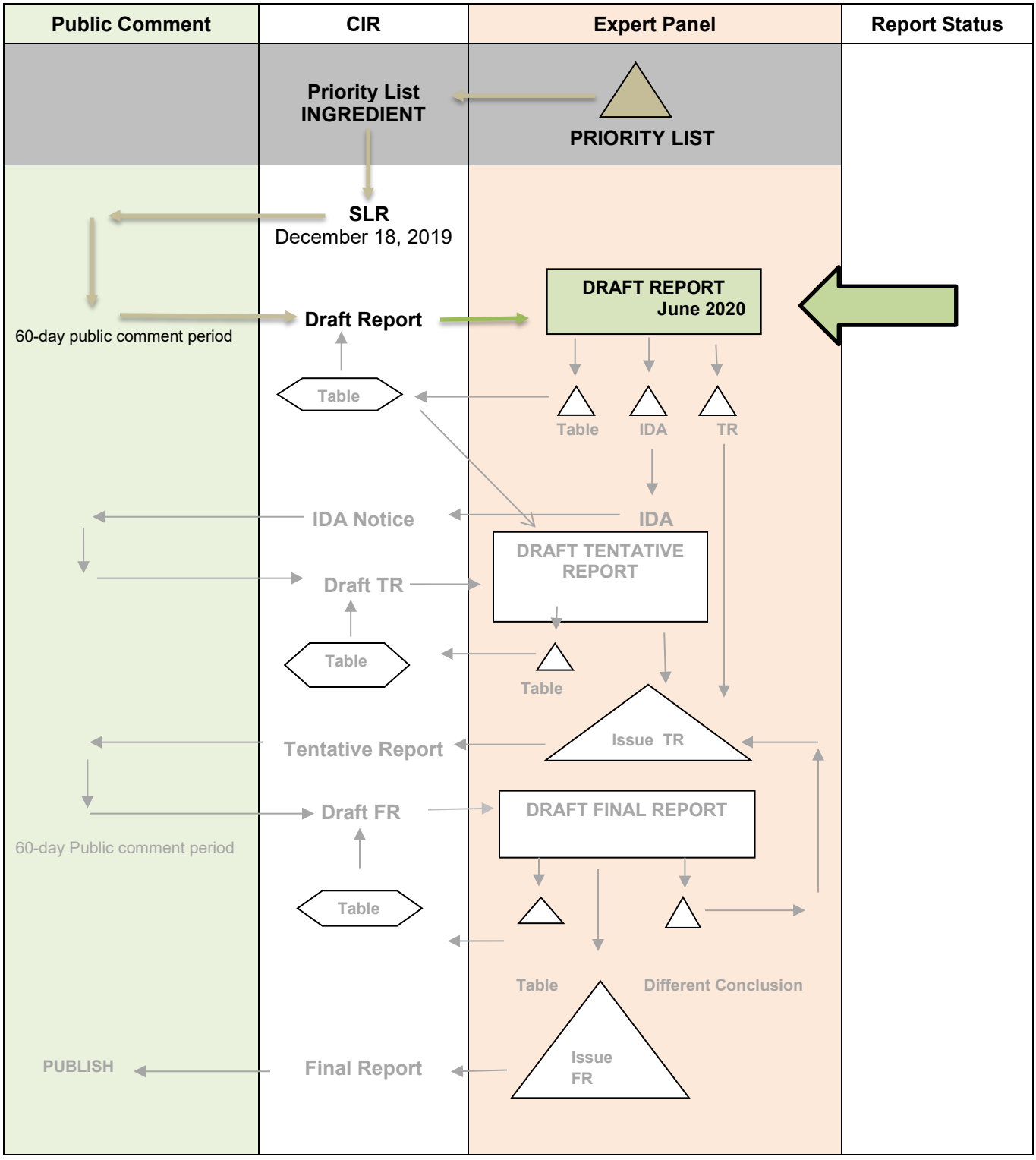
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY ___ Tris(Tetramethylhydroxypiperidinol) Citrate

MEETING ___ June 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 CIR sought the following information:

- 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.

June 2020

-A Draft Report is being presented to the Panel.

Tris(Tetramethylhydroxypiperidinol) Citrate Data Profile* – June 8-9th, 2020 – 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
Tris(Tetramethylhydroxypiperidinol) Citrate	X			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
Tris (Tetramethylhydroxy piperidinol) Citrate	220410-74-2 CosIng: 429-370-5	✓	0/0	✓*	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)

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INTRODUCTION

This is a safety assessment of Tris(Tetramethylhydroxypiperidinol) Citrate as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Tris(Tetramethylhydroxypiperidinol) Citrate is reported to function in cosmetics as a light stabilizer.[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 as used 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] 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

Tris(Tetramethylhydroxypiperidinol) Citrate (CAS No. 220410-74-2) is the salt that conforms to the structure shown in Figure 1.[1]

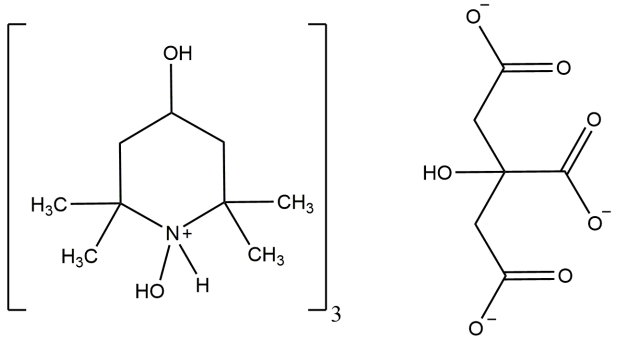

Figure 1. Tris(Tetramethylhydroxypiperidinol) Citrate

Physical and Chemical Properties

Tris(Tetramethylhydroxypiperidinol) Citrate is soluble in water and exhibits a high topological polar surface area (computed value) of 263 Å^2.[4] The physical and chemical properties of Tris(Tetramethylhydroxypiperidinol) Citrate are further outlined in Table 1.

Method of Manufacture

Method of manufacture data were not found in the published literature, and unpublished data were not submitted.

Impurities

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

USE

Cosmetic

The safety of the cosmetic ingredient 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 this ingredient in cosmetics. Use frequencies of individual ingredient 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 Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2020 VCRP survey data, Tris(Tetramethylhydroxypiperidinol) Citrate is reported to be used in 388 formulations, most of which are leave-on formulations (335 uses; Table 2).[5] The results of the concentration of use survey conducted by the Council indicate that the maximum use concentration of this ingredient in leave-on dermal products is 0.05% in cologne and toilet waters. [6]

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 maximum reported 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.[7, 8] 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.[9, 10]

Tris(Tetramethylhydroxypiperidinol) Citrate is not restricted from use in any way under the rules governing cosmetic products in the European Union.[11]

Non-Cosmetic

Non-cosmetic uses were not found in the published literature, and unpublished data were not submitted.

TOXICOKINETIC STUDIES

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

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

An acute dermal toxicity study was performed in accordance with Organization for Economic Co-operation and Development (OECD) test guideline (TG) 402.[3] Two limit tests were performed in which a group of 5 male and 5 female New Zealand White rabbits received one of two dosages of Tris(Tetramethylhydroxypiperidinol) Citrate (93.64% pure) via dermal application covering approximately 10% of the body surface area. The rabbits were exposed to an occlusive patch 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, for 24 h. The rabbits were observed for mortality and clinical abnormalities 14 d before euthanization. No mortality occurred during the observation period. Clinical abnormalities included small feces, soft/mucoid stools, fecal stain, and dark material around the facial area. Dermal irritation was observed at the site of test article application. No significant gross internal findings were observed in the rabbits at necropsy. Under the conditions of this test, the acute dermal LD_{50} was determined to be greater than 2136 mg/kg bw.

Oral

In a single-dose oral toxicity study performed in accordance with OECD TG 401, groups of 5 male and 5 female Sprague-Dawley rats were dosed with Tris(Tetramethylhydroxypiperidinol) Citrate in deionized water by gavage.[3] 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. There were no controls in this study. All study animals were observed for mortality or clinical abnormalites for 14 d after exposure. One male dosed with 2136 mg/kg, 4 dosed with 2670 mg/kg, all males dosed with 3204 mg/kg, and all females dosed with 1602 and 2136 mg/kg Tris(Tetramethylhydroxypiperidinol) Citrate, died; mortality occurred on day 1. (There was no mortality reported in the lower dose groups that died.) The most notable clinical abnormalities observed during the study included decreased activity, convulsions, wobbly gait, breathing abnormalities, prostation, decreased defecation, soft stools, piloerection, apparent hypothennia, blue skin tone, hunched posture, urine/fecal stain, partially closed eyelids, salivation, dilated pupils, ocular discharge, and dark material around the facial area. Gross internal pathologies noted in animals that died prematurely included abnormal digestive tract content, stained mucosa in the stomach, and dark red lungs, while gross internal findings observed at necropsy included three incidences of gray raised area(s) on the lungs in the 2136 mg/kg bw male rats. The acute oral LD_{50} of the test substance in the male rat was determined to be 2495 mg/kg bw, and the oral LD_{50} was estimated to be between 1068 and 1602 mg/kg bw in the female rat. The oral LD_{50} for both sexes was determined to be 1758 mg/kg bw.

Inhalation

An acute inhalation study was conducted according to OECD TG 403 in rats.[3] Five male and 5 female Sprague-Dawley rats were exposed nose-only for 4 h to a fine white powder, composed of 94.8%Tris(Tetramethylhydroxypiperidinol) Citrate, 3.8% water, and 0.6% other, which was aerosolized in a gravimetric chamber at a concentration of 5.08 mg/L. The

estimated mass median aerodynamic diameter (MMAD) was 3.8 µm. The animals were observed for mortality and signs of gross toxicity for 14 d after exposure, and then necropsied. All animals survived the study and and no gross abnormalities were noted upon necropsy. Under the conditions of this study, the acute inhalation LC_{50} was determined to be greater than 5.08 mg/L in male and female rats.

Short-Term Toxicity Studies

Oral

In accordance with OECD TG 407, groups of 5 male and 5 female Sprague-Dawley rats were exposed to 0 (control), 100 (low), 500 (mid), and 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-day 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 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 wks, and were observed for 4 wks 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. Abberations 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 no-observed-adverse-effect-level (NOAEL) for cutaneous application of the test substance was determined to be 150 mg/kg bw/d.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

No developmental or reproductive toxicity studies were found in the published literature, and unpublished data were not submitted.

GENOTOXICITY

In Vitro

The mutagenicity of Tris(Tetramethylhydroxypiperidinol) Citrate (93.64% pure) was evaluated in *Salmonella typhimurium* TA 1535, TA 1537, TA 98, TA 100) and *Escherichia coli* WP2 uvr A, using an Ames, mammalian-microsome reverse mutation assay, in accordance with OECD TG 471.[3] The assay was conducted with five doses of the test article (100, 333, 1000, 3330, 5000 µg per plate) in both the presence and absence of metabolic activation. The results of this assay indicated that the the test substance did not cause a positive increase in the mean number of revertants per plate with any of the tested strains either in the presence or absence of metabolic activation. Concurrent vehicle (dimethyl sulfoxide (DMSO)) and appropriate positive controls gave expected results.

The ability of Tris(Tetramethylhydroxypiperidinol) Citrate to induce chromosomal aberrations in Chinese hamster ovary (CHO) cells, with and without metabolic activation, was tested according to OECD TG 473.[3] The test substance was dissolved in cell culture grade water at concentrations up to 5000 µg/mL, with and without metabolic activation. Except for a weak increase in cells with chromosomal aberrations at 5000 µg/mL in the non-activation assay, no significant increase in cells with chromosomal abnormalities, polyploidy, or endoreduplication was observed.

In Vivo

A micronucleus assay was performed with Tris(Tetramethylhydroxypiperidinol) Citrate (93.64% pure), in accordance with OECD TG 474.[3] Groups of 6 CD-1 male mice were dosed intravenously with 50, 100, or 200 mg/kg bw of the test article in sterile water and had bone marrow harvested after 24 or 48 h of exposure. A concurrent vehicle and positive control (cyclophosphamide, given orally) group were also used. Five animals from the 50 and 100 mg/kg bw dose groups and 5 animals from the positive control group were euthanized approximately 24 h after dosing for bone marrow extraction. Five animals from the 200 mg/kg bw dose group and five animals from the the vehicle control group were euthanized approximately 24 and 48 h after dosing for bone marrow extraction. Clinical toxicity was observed in the 200 mg/kg animals, and 2 animals from this dosing group died. However, the test item did not induce a statistically significant increase in the frequency of micronucleated polychromatic erythrocyte sand was therefore considered non-clastogenic.

CARCINOGENICITY STUDIES

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

DERMAL IRRITATION AND SENSITIZATION

Irritation

Animal

The dermal irritation potential of aqueous Tris(Tetramethylhydroxypiperidinol) Citrate (93.64% pure) was evaluated in 3 male and 3 female New Zealand white rabbits, in accordance with OECD TG 404.[3] The test article (0.5 g) was applied for 4 h to 1 in^2 of shaved skin using a semi-occlusive patch. The test sites were washed with deionized water after exposure, dried with gauze, and observed for up to 7 days following patch removal. A 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 the European Commision (EC) Regulation No. 1272/2008 criteria for Classification, Labelling, and Packaging (CLP), the test item was considered non-irritating, based on both the erythema and edema score.

Sensitization

Animal

A guinea pig maximization test was performed in accordance to OECD TG 406.[3] Ten male and 10 female Hartley albino guinea pigs received intradermal injections of 5.0% Tris(Tetramethylhydroxypiperidinol) Citrate in deionized water, along with injections of Freund's Complete Adjuvant (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, patches with undiluted test article were applied to the test animals for 48 h, and deionized water was applied to the controls. Challenge applications were made with undiluted test article on day 20, using Hilltop chambers. Rechallenge applications were made 8 days later in test and control groups. Group mean dermal scores were noted to be similar in test animals compared with the challenge control animals. Tris(Tetramethylhydroxypiperidinol) Citrate was not considered a sensitizer.

Human

A modified Draize test for dermal sensitization was completed in 104 human subjects.[3] Subjects were exposed to an occlusive patch containing 0.2 mL of 0.1% or 0.5% Tris(Tetramethylhydroxypiperidinol) Citrate in distilled water, for 24 h, three times per week for 3 wks. The control was distilled water or 0.1% aqueous sodium lauryl sulfate. The test site was wiped with water after each testing phase. After a rest period of 10 - 17 days, a previously unexposed site was challenged with Tris(Tetramethylhydroxypiperidinol) Citrate for 24 h. Three adverse events were reported during the course of the study, but they were not related to exposure to the test substance. Furthermore, the test substance did not appear to cause significant irritation potential during the 3-wk induction period or during the challenge phase of the study.

OCULAR IRRITATION

Animal

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 0.027g (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 days following dosing. The mean irritation score was 0.78 (maximum score of 3), and irritation was fully

reversible 72 h to 10 days 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*, Tris(Tetramethylhydroxypiperidinol) Citrate is reported to function in cosmetics as a light stabilizer. In 2020, VCRP data indicate that it is used in 388 formulations, and the highest reported concentration of use is 0.05% (in cologne and toilet waters and in bath soaps and detergents).

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 greater than 2136 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 LD_{50} for both sexes 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 LC_{50} was determined to be greater than 5.08 mg/L.

In a repeated 28-d oral toxicity study, 60 Sprague-Dawley rats received up to 1000 mg/kg bw of Tris(Tetramethyl-hydroxypiperidinol) Citrate via gavage. Dose-dependent clinical abnormalities observed included increased serum bilirubin, statistically significant decrease in red blood cell counts, haemoglobin, and hemocrit. 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 13-wk dermal toxicity study, 100 Wistar Han rats were exposed to an open application of up to 500 mg/kg bw/d, 97.3% pure Tris(Tetramethylhydroxylpiperidinol) Citrate. Scabs were noted at the application site during the treatment; chorioretinopathy, aberrations in glucose, urea, white blood cell count, and potassium concentration were also observed, but were mostly reversible during the treatment-free period. Based on the results of this study, the NOAEL was determined to be 150 mg/kg bw/d.

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. Tris(Tetramethylhydroxypiperidinol) Citrate was not clastogenic in a mouse micronucleus assay, in which mice were intravenously dosed with up to 200 mg/kg bw of the test substance.

Undiluted Tris(Tetramethylhydroxypiperidinol) Citrate 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; a mean erythema score of 1 and mean edema score of 0 was reported. 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 an irritant or 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 days.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. Physical and Chemical Properties of Tris(Tetramethylhydroxypiperidinol) Citrate

Property	Value	Reference
Physical Form (@ 20°C & 1013 hPa)	Solid	[3]
Formula Weight (g/mol)	711.9	[4]
Topological Polar Surface Area (Å^2)	263 (calculated)	[4]
Density/Specific Gravity (g/mL @ 24 ºC)	1.190	[3]
Vapor pressure (Pa @ 20ºC)	< 0.6	[3]
Melting Point (ºC)	59.17 - 64.26	[3]
Boiling Point (ºC)	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 @ 20.5ºC)	> 500	[3]

Table 2. Frequency (2020) and concentration (2018) of use of Tris(Tetramethylhydroxypiperidinol) Citrate

	# of Uses[5]	Max Conc of Use (%)[6]
Totals*	**388**	**0.0001-0.05**
Duration of Use		
Leave-On	*335*	*0.0001-0.05*
Rinse-Off	*44*	*0.005-0.05*
Diluted for (Bath) Use	*9*	*NR*
Exposure Type		
Eye Area	5	0.005
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	154; 138[a]; 26[b]	0.0001-0.05; 0.0001-0.01[a]
Incidental Inhalation-Powder	26[b]; 1[c]	0.005-0.01[c]
Dermal Contact	372	0.0001-0.05
Deodorant (underarm)	2[a]	Not spray: 0.01
Hair - Non-Coloring	15	0.0001-0.01
Hair-Coloring	1	0.005
Nail	NR	NR
Mucous Membrane	31	0.01-0.05
Baby Products	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

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2020 FDA Frequency of Use Data – 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

2020 FDA Frequency of Use Data – Total: 388

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 - Tris(Tetramethylhydroxypiperidinol) Citrate

Product Category	Maximum Concentration of Use
Eye lotions	0.005%
Colognes and toilet waters	0.02-0.05%
Other fragrance preparations	0.01%
Hair conditioners	0.005%
Shampoos (noncoloring)	0.005%
Tonics, dressings and other hair grooming aids	0.0001-0.01%
Hair dyes and colors	0.005%
Bath soaps and detergents	0.01-0.05%
Deodorants	
Not spray	0.01%
Aftershave lotions	0.005-0.01%
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.01%
Face and neck products	
Not spray	0.005%
Body and hand products	
Not spray	0.01%
Spray	0.0001%
Moisturizing products	
Not spray	0.003%

Information collected in 2018

Table prepared June 1, 2018

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: January 16, 2020

SUBJECT: Scientific Literature Review: Safety Assessment of Tris(Tetramethylhydroxypiperidinol) Citrate as Used in Cosmetics (release date: December 18, 2019)

The Personal Care Products Council respectfully submits the following comments on the scientific literature review, Safety Assessment of Tris(Tetramethylhydroxypiperidinol) Citrate as Used in Cosmetics.

Key Issue

The Toxicokinetic section does not accurately reflect what is stated in the ECHA dossier. The ECHA dossier indicates that Tris(Tetramethylhydroxypiperidinol) Citrate is made of two components, at a ratio of 3 to 1. Therefore, the "main component" is tetramethylhydroxypiperidinol and the "minor component" is citric acid. This is consistent with the description of the "minor component" as a weak acid. Therefore, "(not specified)" after major and minor component should be deleted. The statement in the CIR report: "It is not expected that Tris(Tetramethylhydroxypiperidinol) Citrate will penetrate the skin." is not what the ECHA dossier concluded. Based on observed adverse effects in the dermal studies, the ECHA dossier (in the conclusion of the toxicokinetics section) states: "Based on the results of the experimental investigations as well as on the molecular weight and physico-chemical properties the test item is considered to be bioavailable via oral, inhalation and dermal route." This ECHA conclusion also states that "The minor component is a metabolic intermediate vital to the TCA respiration pathway [citric acid cycle]." further implying that citric acid is the minor component.

Additional Considerations

Introduction - The Introduction should mention the CIR report on Citric Acid and salts (published in 2014) with a conclusion of safe as used.

Physical and Chemical Properties - It should be stated that the polar surface area is a computed value.

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Cosmetic Use - Please state the product categories in which Tris(Tetramethylhydroxypiperidinol) Citrate is used at the maximum reported use concentration.

Genotoxicity, In vitro - What happened in the "confirmatory" Ames assay?

Ocular Irritation - As this ingredient is a solid, it would be helpful to also include the weight of dose ("determined to be 0.0270 g") of the test material instilled into rabbit eyes.

Summary - Please correct: "skn"

Table 1 - It should be stated that the partition coefficient is actually LogKow (log of the octanol/water partition coefficient) and that this value was determined experimentally.