Safety Assessment of Copper Gluconate as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	February 14, 2025
Panel Meeting Date:	March 13 - 14, 2025

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.; Samuel Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Thomas J. Slaga, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Preethi Raj, M.Sc., former Senior Scientific Analyst/Writer, and Christina Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

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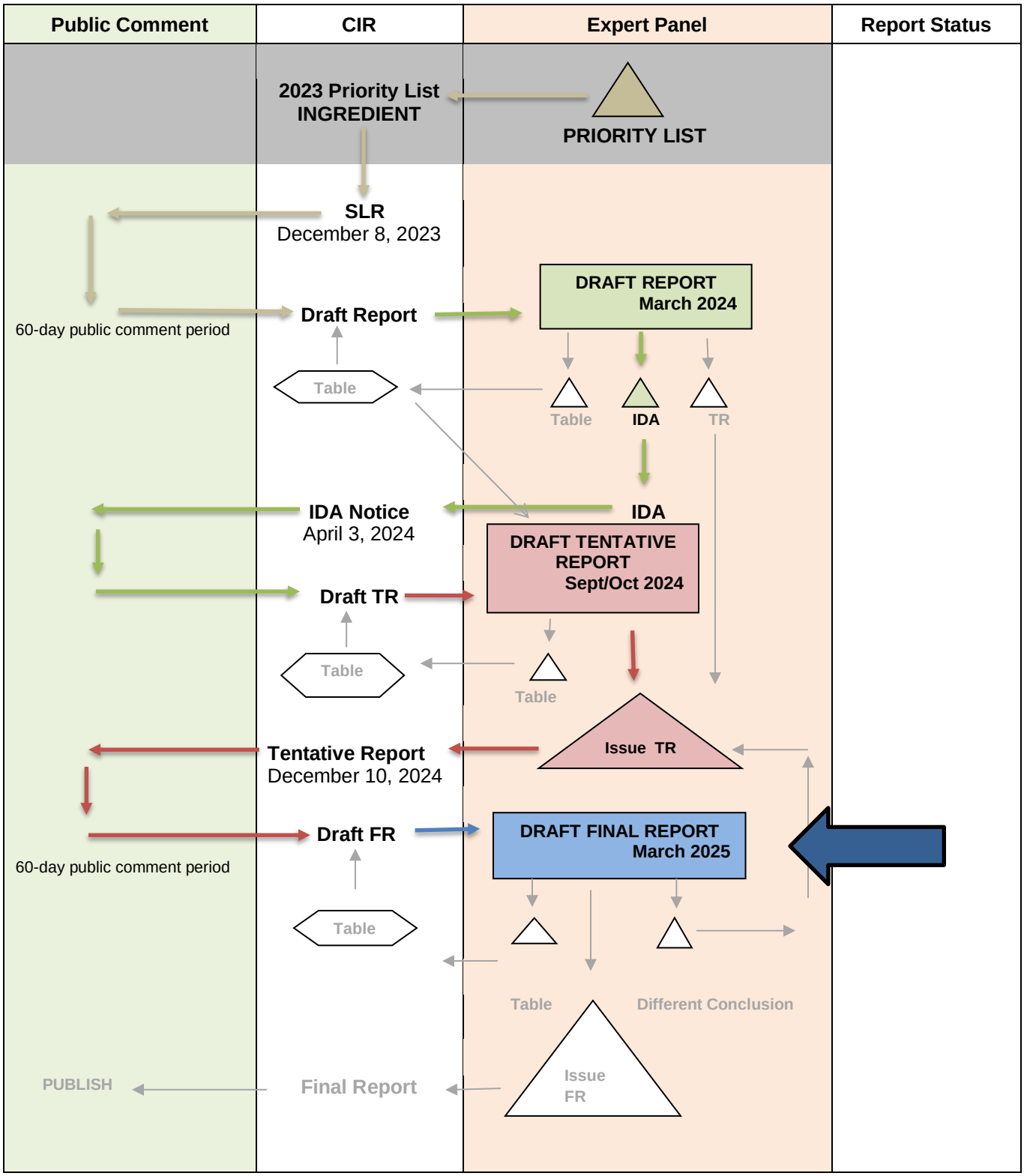
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Copper Gluconate

MEETING March 2025



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, M.S., Senior Scientific Analyst/Writer, CIR
Date: February 14, 2025
Subject: Safety Assessment of Copper Gluconate as Used in Cosmetics

Enclosed is the Draft Final Report on Copper Gluconate as Used in Cosmetics. (It is identified as *report_CopperGluconate_032025* in the pdf document). At the September 2024 meeting, the Panel issued a Tentative Report for public comment with the conclusion that Copper Gluconate is safe for use as a cosmetic ingredient in the present practices of use and concentration described in the safety assessment.

Since the September meeting, no new data have been received or identified in an updated literature search. Comments provided by the Council on the draft Tentative Report received prior to the September 2024 Panel meeting (*PCPCcomments1_CopperGluconate_032025* and *response-PCPCcomments1_CopperGluconate_032025*) and on the Tentative Report released for public comment after the meeting (*PCPCcomments2_CopperGluconate_032025* and *response-PCPCcomments2_Gluconate_032025*) have been addressed.

The report has been updated with RLD that were received in 2024. According to the RLD, Copper Gluconate is used in 666 formulations, with the majority of the uses reported in skin care preparations (492 uses, with the highest concentration of use reported at 0.1% in rinse-off cleansing products and 0.008% in leave-on night products). This new data along with the informational text on Wilson's disease and Menkes disease have been highlighted to aid with the Panel's review.

Additional supporting documents for this report package include the flow chart (*flow_CopperGluconate_032025*), report history (*history_CopperGluconate_032025*), a search strategy (*search_CopperGluconate_032025*), a data profile (*dataprofile_CopperGluconate_032025*), and the transcripts from the previous Panel deliberations (*transcripts_CopperGluconate_032025*).

The Panel should carefully review the Abstract, Discussion, and Conclusion, and issue a Final Report.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: September 23, 2024

SUBJECT: Draft Tentative Report: Safety Assessment of Copper Gluconate as Used in Cosmetics (draft prepared for the Sept 30-Oct 1, 2024, CIR meeting)

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

Key Issues

Although the Introduction states: "Thus, the primary focus of the safety assessment of this ingredient as used in cosmetics is on the potential for local effects from topical exposure" there is not much information about sensitization included in the report. As copper is the component of concern regarding dermal sensitization, please add some information about the dermal sensitization potential of copper (generally patch tested as copper sulfate). Perhaps the following review would be helpful: Hostynek JJ, Maibach HI. 2004. Copper hypersensitivity: dermatologic aspects. Review Dermatol Ther 17(4):328-33. doi: 10.1111/j.1396-0296.2004.04035.x.

Exposure Assessment – If systemic toxicity is not a concern, is estimating mg/kg exposure necessary for Copper Gluconate? If the Exposure Assessment section is left in the report, primary references should be cited for the use information.

If the Exposure Assessment section is left in the report it needs to made clear that the "other oral hygiene product" is not a mouthwash because there is a mouthwash category that could have been selected. No exposure estimate should be provided for this product.

It should also be made clear that the surface area of the body to which the night product is applied is not known, so whole-body exposure is being used as a conservative approach.

Additional Considerations

Introduction – The last sentence of the Introduction needs to be revised to make it clear that ECHA has "summaries of information generated by industry". Currently, the last sentence also

implies that the INCHEM/JECFA data are generated by industry. This is not correct.

Impurities – If available, please identify the elements measured for the information from reference 11.

Cosmetic Use; Summary – The PCPC concentration of use survey was completed in 2022 with updates/revisions completed in 2024. It is not accurate to state that it was conducted in 2024.

Acute – Because it was a single dose exposure, “after 7 d of exposure” should be “7 d after exposure” (if “after 7 d of exposure” is correct, the exposure for this 7-day study should be described).

Discussion – The Discussion should also note that copper is essential.

Copper Gluconate – March 2025 – Christina Burnett	
Comment Submitter: Alexandra Kowcz, Personal Care Products Council **Date of Submission: September 23, 2024**	
Comment	**Response/Action**
Key Issue - Although the Introduction states: "Thus, the primary focus of the safety assessment of this ingredient as used in cosmetics is on the potential for local effects from topical exposure" there is not much information about sensitization included in the report. As copper is the component of concern regarding dermal sensitization, please add some information about the dermal sensitization potential of copper (generally patch tested as copper sulfate). Perhaps the following review would be helpful: Hostynek JJ, Maibach HI. 2004. Copper hypersensitivity: dermatologic aspects. Review Dermatol Ther 17(4):328-33. doi: 10.1111/j.1396-0296.2004.04035.x.	There are 4 HRIPTs for Copper Gluconate (0.00008 - 0.2%) in this report with 52 - 217 subjects. All results were non-irritating/non-sensitizing. Dr. Heldreth instructed that this comment be ignored.
Key Issue - Exposure Assessment – If systemic toxicity is not a concern, is estimating mg/kg exposure necessary for Copper Gluconate? If the Exposure Assessment section is left in the report, primary references should be cited for the use information. If the Exposure Assessment section is left in the report it needs to made clear that the "other oral hygiene product" is not a mouthwash because there is a mouthwash category that could have been selected. No exposure estimate should be provided for this product. It should also be made clear that the surface area of the body to which the night product is applied is not known, so whole-body exposure is being used as a conservative approach.	Several revisions were made to Exposure Assessment of the Tentative Report, but two comments were missed and further revisions were made to the draft Final Report. The primary references have been added. The exposure estimate for oral products was deleted.
Introduction – The last sentence of the Introduction needs to be revised to make it clear that ECHA has "summaries of information generated by industry". Currently, the last sentence also implies that the INCHEM/JECFA data are generated by industry. This is not correct.	Paragraph revised to the current boilerplate language and reference to INCHEM was deleted.
Impurities – If available, please identify the elements measured for the information from reference 11.	As there were 24 elements listed in the refence, sentence was revised to
Cosmetic Use; Summary – The PCPC concentration of use survey was completed in 2022 with updates/revisions completed in 2024. It is not accurate to state that it was conducted in 2024.	Revision made.
Acute – Because it was a single dose exposure, "after 7 d of exposure" should be "7 d after exposure" (if "after 7 d of exposure" is correct, the exposure for this 7-day study should be described).	Corrected.
Discussion – The Discussion should also note that copper is essential.	Revision made.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 2, 2025

SUBJECT: Tentative Report: Safety Assessment of Copper Gluconate as Used in Cosmetics (release date: December 10, 2024)

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

Abstract; Discussion – There is no information in the CIR report about EPA "limits" relevant to Copper Gluconate. Therefore, the mention of EPA limits in the Abstract and Discussion should be deleted.

Exposure Assessment – For the dermal products (skin cleansing and night products), it is not clear why it states: "SED with 100% absorption (oral absorption)". Perhaps it should still assume 100% absorption, but state it is dermal absorption for these products used on the skin.

Discussion – The Discussion is misleading when it states: "carcinogenicity data from dietary studies on Copper Gluconate are available." The only carcinogenicity studies on Copper Gluconate in the CIR report are oral tumor promotion studies that used high doses of Copper Gluconate. The Discussion should clearly state the type of study available.

Table 5, reference 28 – Rather than "not specified" in the Vehicle column it could state distilled water (or just aqueous) as the study states: "STOCK SOLUTIONS; Were prepared from 99.5% DMSO for disulfiram and distilled water for copper gluconate" and that one control group received saline.

Copper Gluconate – March 2025 – Christina Burnett	
Comment Submitter: Alexandra Kowcz, Personal Care Products Council **Date of Submission: January 2, 2025**	
Comment	**Response/Action**
Abstract; Discussion – There is no information in the CIR report about EPA "limits" relevant to Copper Gluconate. Therefore, the mention of EPA limits in the Abstract and Discussion should be deleted.	This was wording the Panel asked to be put into the report. Until directed otherwise, the wording stays in place.
Exposure Assessment – For the dermal products (skin cleansing and night products), it is not clear why it states: "SED with 100% absorption (oral absorption)". Perhaps it should still assume 100% absorption, but state it is dermal absorption for these products used on the skin	Deleted "(oral absorption)".
Discussion – The Discussion is misleading when it states: "carcinogenicity data from dietary studies on Copper Gluconate are available." The only carcinogenicity studies on Copper Gluconate in the CIR report are oral tumor promotion studies that used high doses of Copper Gluconate. The Discussion should clearly state the type of study available.	Sentence revised.
Table 5, reference 28 – Rather than "not specified" in the Vehicle column it could state distilled water (or just aqueous) as the study states: "STOCK SOLUTIONS; Were prepared from 99.5% DMSO for disulfiram and distilled water for copper gluconate" and that one control group received saline.	Replaced "not specified" with "distilled water".

CIR History of:

Copper Gluconate

July 2022

-Concentration of use data submitted by Council

January 2023

-FDA frequency of use data obtained

December 2023

-Copper Gluconate SLR posted on the CIR website

No new data were received.

March 2024

A Draft Report was being presented to the Panel for review. The Panel issued an IDA for the following data needs:

- Impurities data for Copper Gluconate as used in cosmetics •
- Dermal irritation and sensitization data at maximum concentration of use
- Ocular irritation data, if available

April, May, and July 2024

The following data were received in response to the IDA:

- Updated concentration of use data (submitted by Council)
- Copper Gluconate purity information, and regulatory statements for impurities
- 4 HRIPTs testing products containing up to 0.2% Copper Gluconate
- An in vitro ocular irritation test of a face cream containing 0.0025% Copper Gluconate

September/October 2024

The Panel issued a Tentative Report for public comment with the conclusion that Copper Gluconate is safe for use as a cosmetic ingredient in the present practices of use and concentration described in the safety assessment.

Copper Gluconate Data Profile* – March 2025 – Writer, Christina Burnett																														
				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
Copper Gluconate	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

[Copper Gluconate]

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Copper Gluconate	527-09-3	✓	✓	✓	NR	NR	✓	NR	NR	✓	NR	NR		✓*	NR		

Search Strategy – updated 08/13/2024

((((((((((((Copper Gluconate) OR (Bis(D-Gluconato)Copper)) OR (Copper, Bis(D-Gluconato)-)) OR (Cupric Gluconate)) OR (Gluconic Acid, Copper Salt)) OR (Actibronze)) OR (Cutein)) OR (Glycosnail VEG)) OR (Sepitonic M3)) OR (Sepitonic M4)) OR (Givobio GCu)) OR (Gluconal CU)) OR (OriStar CGC)) OR (527-09-3) – 88,516 hits/4 useful

LINKS

Search Engines

- Pubmed - http://www.ncbi.nlm.nih.gov/pubmed
  - appropriate qualifiers are used as necessary
  - search results are reviewed to identify relevant documents
- Connected Papers - https://www.connectedpapers.com/

Pertinent Websites

- wINCI - https://incipedia.personalcarecouncil.org/winci/ingredient-custom-search/
- FDA Cosmetics page - https://www.fda.gov/cosmetics
- eCFR (Code of Federal Regulations) - https://www.ecfr.gov/
- FDA search databases: https://www.fda.gov/industry/fda-basics-industry/search-databases
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras
- SCOGS database: https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database
- Inventory of Food Contact Substances Listed in 21 CFR: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives
- Drug Approvals and Database: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases
- FDA Orange Book: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
- OTC Monographs - https://dps.fda.gov/omuf
- Inactive Ingredients Approved For Drugs: https://www.accessdata.fda.gov/scripts/cder/iig/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- EUR-Lex - https://eur-lex.europa.eu/homepage.html
- Scientific Committees (SCCS, etc) opinions: https://health.ec.europa.eu/scientific-committees_en https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en
- ECHA (European Chemicals Agency – REACH dossiers) – https://echa.europa.eu/
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- EFSA (European Food Safety Authority) - https://www.efsa.europa.eu/en
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- Office of Dietary Supplements https://ods.od.nih.gov/
- 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) IRIS library - https://apps.who.int/iris/
- a general Google and Google Scholar search should be performed for additional background information, to identify references that are available, and for other general information - www.google.com https://scholar.google.com/

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/
- 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 (2nd Edition; 2013) - http://abc.herbalgram.org/site/DocServer/AHPABotanicalSafety_FMexcerpt.pdf?docID=4601
- 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) – https://ifrafragrance.org/
- Research Institute for Fragrance Materials (RIFM) - https://www.rifm.org/#gsc.tab=0 http://fragrancematerialsafetyresource.elsevier.com/
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MARCH 2024 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – March 28, 2024

DR. BELSITO: Here we have a Wave 2 comments from PCPC. I won't go through all the comments, but I agreed with them all. Did anyone have any disagreement with the Council's comments?

DR. SNYDER: I did not.

DR. KLAASSEN: No.

DR. RETTIE: No, they're fine.

DR. BELSITO: Right. Basically, this is the first time we're looking at this ingredient. An SLR was announced in December of 2023. We previously looked at gluconic acid, potassium gluconate, and sodium gluconate. In 2019 the final report was published with a conclusion that these ingredients are safe in the present practice of use and concentration in cosmetics, but we have never looked at copper.

In terms of impurities, we have -- well, looking at the document, the first impurities we have -- the purity of food-grade copper is said to be 98 to 102 percent. Limits for reducing substances is one percent. No other impurities data, so my question is, as we go forward, are we assuming that copper in cosmetics is food-grade in terms of the impurities? If so, we should state that in the discussion, or do we want impurities data for cosmetic-grade copper gluconate? Paul? Curt? Allan?

DR. SNYDER: Well, I took that impurities section, Don, just for them to say that was the only impurities data there was. I mean, not necessarily the -- so, I mean, that's the only impurities data we have.

DR. BELSITO: I know, but is it sufficient? I mean, we could just keep this angle and say it's insufficient for impurities data and give it to those guys. Are we going to do that, or are we going to assume that that's the data for cosmetic-grade?

DR. SNYDER: Well, again, we're talking about, for leave-ons, a 0.006 percent in eyeliners. It's an essential element. I mean, I didn't -- it didn't raise any red flags to me. I'll say that.

DR. BELSITO: Curt? Allan?

DR. RETTIE: Yeah, I was the same --

DR. BELSITO: I mean, what difference (audio skip) fault, not having impurities data on the cosmetic-grade or the impurities on food-grade?

DR. SNYDER: Impurities data in any context. It's only 0.006 percent. I mean, I couldn't even guess what a impurity might be in there that would be of concern. I mean, copper is a liver and kidney toxin at high levels, but I don't -- yeah. I guess I'd put it onto Curt. I mean, he has more experience in these types of questions than me.

DR. KLAASSEN: Yeah, again, the concentrations are quite low. It probably isn't absorbed well. There is one concern, theoretical concern, with copper. There are people that are genetically susceptible to copper toxicity called Wilson's disease.

DR. BELSITO: Mm-hmm.

DR. KLAASSEN: Yeah, I'm not overly concerned about that. It might be nice to at least mention that in the text, that there is -- some people are genetically susceptible. We do get copper exposure in our drinking water as water is going through copper pipes today. Copper isn't, well, a real -- as far as metals are concerned, copper is relatively non-toxic. It's not like a mercury or a lead or a chromium or a cadmium.

DR. BELSITO: I understand, but it's a mined mineral. Are we not concerned about, perhaps, a toxic substance that is 50 percent of cosmetic-grade copper? We don't have data on cosmetic-grade.

DR. KLAASSEN: Well, I think we should ask for it. Can we ask for it now?

DR. BELSITO: Yeah. I mean, this is the first time we're seeing it.

DR. KLAASSEN: Okay, that's what I thought. Let's ask for it.

DR. BELSITO: Okay.

DR. KLAASSEN: Also, what it's like -- in the cosmetic grade, what are the impurities?

DR. BELSITO: Okay. I'm fine with that.

DR. RETTIE: I mean, is it established that there's a cosmetic-grade separate from the regular grade?

DR. BELSITO: I don't know.

MS. FIUME: No, there's --

DR. KLAASSEN: We don't --

DR. BELSITO: They specifically said food-grade.

MS. FIUME: The term cosmetic-grade in the U.S. does not exist. Nothing is cosmetic grade.

DR. BELSITO: Right. We're ask --

MS. FIUME: It may be used in cosmetics, but.

DR. BELSITO: We're asking for the impurities in copper gluconate as used in cosmetics.

DR. RETTIE: Is the likelihood that what comes back from that is the impurities that we have already in the document here?

DR. BELSITO: We really have no impurities other than it says that the limit for reducing agents is one percent. I don't even know what the reducing agent is.

DR. RETTIE: Well, they put limits on lead in the food-grade on reducing substances.

DR. BELSITO: I couldn't hear what you said, Allan.

DR. RETTIE: Well, I'm just reading the impurities section, and there are limits for the food-grade copper of no more than five mgs per kgs in lead in a gram, and, similarly, some information on the limit for reducing substances of one percent.

DR. BELSITO: Right. What is the reducing substance?

DR. RETTIE: That's not specified.

DR. BELSITO: Yeah, I mean, this is the first time we're seeing it.

DR. RETTIE: Yeah, sure. Absolutely. We can ask for more.

DR. BELSITO: I (audio skip) what the impurities are there.

DR. RETTIE: Yeah.

DR. BELSITO: Paul is right. The leave-on is 0.006 percent in the eyeliner, 0.2 percent in the baby shampoo for rinse-off.

Then, under Exposure Assessment, they have 0.0025 percent in a body lotion, 0.1 percent in a makeup remover. That's because of, I'm assuming, we're now doing the systemic exposure based upon not only concentration, but body surface area to what it's applied. It's not entirely clear, even though it says, "product category with a higher level of exposure." I think it needs to -- I mean, it assumes we've read the exposure report and know where we're going with these margins of safety. This is PDF page 20. I think it should sort of say that highest use concentration but product category with a higher level of exposure based upon the concentration and the body surface area to which the product is exposed. It makes it a little clearer. You see what I'm talking about, Monice? It's the second par --

MS. FIUME: I'm sorry. The second paragraph?

DR. BELSITO: Yeah, second paragraph in the exposure assessment, PDF page 20.

MS. FIUME: Yes. Okay.

DR. BELSITO: Just make it clearer that because the highest use concentration, then it says, "or for the product category with the higher level of exposure," I think higher level of exposure based upon concentration of use and extent to which the product is applied to the body surface, or something like that.

DR. KLAASSEN: How is it the retention factor here lies at 0.01? Is that really based on data?

DR. BELSITO: There was --

MS. FIUME: It looks as if Jinqiu Zhu's not online.

DR. BELSITO: I was not part of the QRA subgroup that did that paper in 2008, Curt, so I can't answer how they came up with those retention factors and product categories. I don't even know if it was totally spelled out in the 2008 QRA paper how they came up with those retention factors.

I think I have a copy of it here. Let me see if I can pull it up. Okay. Oh, here it is. Retention factor. Yeah. Yeah. It never said how they came up with the retention factors. They just applied these retention factors.

I mean, I can tell you what they are by product category. Deodorants and antiperspirants are one. Shaving creams are one. Lip products are four. Eye products are two. Again, based upon increased absorption, body creams and lotions are 0.5. Facial creams for men are two because it's shaved skin. Toothpaste is oral. Rinse-off exposure is two. Mouthwashes are three. Nail care is 0.43. I don't know what the basis for those retention factors are. I'm sorry, I was reading the wrong numbers.

DR. RETTIE: Is it right? Is there any values as low as 0.01?

DR. BELSITO: Yeah.

DR. RETTIE: I'm just wondering if that's (audio skip) relative to 0.1 for other --

DR. BELSITO: 0.01 are -- Allan, let me go through -- are shave creams, depilatories, mouthwashes, shampoos, conditioners, bar soaps, liquid soaps -- they're all wash offs -- face washes, bath gels. So, 0.01 are rinse-off products essentially.

DR. RETTIE: Okay. Yep.

DR. BELSITO: 0.1 are mucosal products and sprays, so mucosa and inhalation.

DR. SNYDER: Monice has a comment, Don.

DR. BELSITO: Go ahead.

MS. FIUME: Don, reading the little paragraph above the values, I believe these may have actually come from Notes of Guidance. I don't see Jinqiu on our call right now. The retention values, I'm not sure if they're exactly the same between RIFM and the Notes of Guidance. I haven't compared it. I think, based on what he has there, he is using the Notes, that retention factors, so they may be similar, they may not. There might be a few discrepancies.

All it says about the retention factor was that it was introduced by the SCC-NFP to take into account rinsing off and dilution of finished products by application on wet skin or hair.

DR. BELSITO: Mm-hmm.

MS. FIUME: Again, it doesn't really, based on my quick look in here, describe how they've come up. As you say, it's rinse-off versus what it's being exposed to. Allan, if you're seeing a discrepancy, if you go back and look at the paper Don's looking at, if you see a discrepancy, that might be why. I'm not sure of the Notes of Guidance. It sounds like they're similar, but there may be a couple that are different.

DR. BELSITO: Yeah.

DR. KLAASSEN: Could those two pa- --

DR. RETTIE: No. I think -- I'm sorry.

DR. KLAASSEN: Are these two different papers that you're talking about? Don has one, and you have another?

MS. FIUME: I have the Notes of Guidance that were issued by the SCCS last year.

DR. KLAASSEN: Okay.

MS. FIUME: Don, is the paper you're referring actually the Api paper? Because the reference they use in Notes of Guidance is Hall (phonetic) et. al.?

DR. BELSITO: No. Mine is the Api paper.

MS. FIUME: It is the Api paper?

DR. BELSITO: I'm going to email it to you now.

DR. KLAASSEN: Yeah, I'd like to see that.

DR. RETTIE: Yeah.

DR. BELSITO: Paul Snyder, why am I not getting your email coming up?

DR. SNYDER: Just klpath@comcast.net -- klpath@comcast.net.

DR. BELSITO: Klpath -- oh, yeah. Okay. Curt --

DR. KLAASSEN: Hey.

DR. BELSITO: -- do you want curtklaassenphd@gmail?

DR. KLAASSEN: Yes. Yes.

DR. BELSITO: Okay. I just sent it.

DR. KLAASSEN: Thank you.

DR. BELSITO: It's page 15 of the paper is where they have the retention factors.

DR. KLAASSEN: Okay.

DR. BELSITO: Basically, I mean, when you look at them, leave-ons get a retention factor of one. Rinse-offs get a retention factor of 0.01 when they're mucosal or potentially inhaled -- well, 0.01, I'm sorry -- 0.1, right, when they're mucosal or potentially inhaled, and 0.01 for rinse-offs that are like shampoos, bath gels, et cetera. Those are pretty much the values.

DR. KLAASSEN: In essence, it's a hundred percent, 10 percent, and one percent.

DR. BELSITO: Right. Then I don't know if -- what was the reference that is in our report? Monice, let me see if it's in the RIFM report. It was Hall, you said?

MS. FIUME: Well, that's in the Notes of Guidance from SCCS. It's Hall et. al., 2007 and 2011.

DR. BELSITO: Okay.

MS. FIUME: Then, also, Stiling et. al., 2012, S-T-I-L-I-N-G.

DR. BELSITO: Yeah, none of those work. Yeah, Squire and Hall, 1985. No. No. They didn't reference them. They referenced a Squire and Hall, 1985 paper for determining the safety assessment factors. Okay. I honestly don't know how they differ.

MS. FIUME: They appear very similar. The Hall papers state, "European consumer exposure to cosmetic products," in both of their titles. It seems to be trying to make it specific to Europe. It seems as if the retention factors are similar. I think the only one I see different is there's one for toothpaste in the Notes of Guidance, and that's 0.05. All the others are 0.01, 0.1, and one.

DR. BELSITO: Yeah. Toothpaste would be a little higher than what RIFM would have at 0.01.

MS. FIUME: Yep.

DR. BELSITO: Okay.

MS. FIUME: Then mouthwash was 0.1.

DR. BELSITO: Okay. Is everyone clear on these retention factors? I mean, be that as it may, we have to know if it's been applied if we're doing absorption based upon --

DR. KLAASSEN: I mean, I think those numbers are realistic. I think they're useful. I'm not sure they're a hundred percent scientific, but they're good enough for risk assessment.

DR. BELSITO: Okay.

DR. KLAASSEN: I mean, we've always said -- we've always made a big deal if this is a wash-off -- the chemical's a wash-off or not.

DR. BELSITO: Mm-hmm.

DR. KLAASSEN: This is kind of giving the quantitative number to that.

DR. BELSITO: Uh-huh. The only issue I have was the exposure in a baby shampoo where they used the adult surface area for the head. We know that the surface area of a baby's head is significantly larger. Then it said that VERMEER Cosmolife calculates daily exposure to baby shampoo using the surface area in an adult. Shouldn't we, though, be using the surface area that the EPA has assumed? Although here it's --

DR. KLAASSEN: One probably should use the surface area of the child rather than the adult. Probably, in the end, it won't make that much difference.

DR. BELSITO: Okay. Then, looking at this entire document, if we knew impurities in the copper gluconate that was used in cosmetics, we could argue that it's GRAS, so we're not concerned about its systemic toxicity which, regardless, is okay. Although the genotox, I think, is a little weak. We also don't have dermal irritation and sensitization.

DR. RETTIE: Right.

DR. BELSITO: I would say that this document is insufficient for impurities, dermal sensitization, and irritation at concentration of use -- and ocular irritation, if available. Otherwise, the systemic endpoints look fine. Curt? Paul?

DR. SNYDER: I agree with the insufficient data announcement at this stage of the document.

DR. BELSITO: Okay. Curt?

DR. KLAASSEN: Yeah, I second that.

DR. BELSITO: Allan?

DR. RETTIE: Yeah, impurities, dermal irritation, and sensitization and ocular irritation seem to cover it.

DR. BELSITO: Okie doke. Any other comments?

MS. FIUME: Just the question about often -- I think it's particularly in ECHA -- there are those QSAR predictions. What are -- do the Panel find -- do you find those useful? Do you want those included? How would you like the writers to handle those

QSAR predictions, an example being under Dermal Irritation and Sensitization on PDF page 20? It's the very bottom paragraph under Dermal Irritation and Sensitization. It's discussing REACH's use of QSAR predictions.

DR. BELSITO: Right. I mean, here I think it's hard to estimate. It says, "...predicts copper gluconate would produce an irritation index of 2.26 in rabbit skin." Then another one with predicting the EC3 in an LLNA of 5.08 copper gluconate. First of all, we don't know what the level of copper that would induce that level of irritation. Is it assume that it's a hundred percent pure copper would cause an irritation index of 2.26? I don't know. Yeah, I think QSARs are nice. To me, just to use them, an In Silico model, to predict irritation and sensitization is not adequate.

MS. FIUME: Do you want these data to remain in the report? Or do you want them removed?

DR. BELSITO: I mean, they can remain in the report for now.

MS. FIUME: Okay.

DR. BELSITO: I would like to see some data on irritation and sensitization at concentrations of use. That --

DR. KLAASSEN: You're talk -- oh, excuse me.

DR. BELSITO: Pardon?

DR. KLAASSEN: I'm lost here. You're talking about page 20?

MS. FIUME: Yes.

DR. BELSITO: Yes, page 20, dermal irritation and sensitization are In Silico predictions --

DR. KLAASSEN: Oh.

DR. BELSITO: -- using a QSAR model.

DR. KLAASSEN: Okay. I see it.

DR. BELSITO: I'm basically saying that for irritation and sensitization I don't think In Silico models are adequate. I mean, I'd take an In Vitro model if they want to give me a DPRA, KeratinoSens, and LuSens or h-CLAT or, you know, but QSAR I have a little trouble with.

MS. FIUME: Yeah. These are just starting to appear in the ECHA dossiers. We're not sure how to use them. We're presenting them, but, again, we didn't know if the Panel even wants them in the report or not.

DR. BELSITO: I think if -- like, take sensitization. If we were relying simply on In Vitro tools, which are still only recently developed, and it would add weight of evidence to a prediction of a sensitizer or a non-sensitizer along with the In Vitro, I'd like to see it. If we have In Vivo data, then I think I really don't care what QSAR says.

MS. FIUME: Okay.

DR. BELSITO: I think it's like everything else. It's a case-by-case basis.

MS. FIUME: It seems to be going that way anymore.

DR. BELSITO: Yeah. Anything else on copper? If not, we're going to move to *t*-Butyl Alcohol.

Cohen Team – March 28, 2024

DR. COHEN: All right. Copper Gluconate. Are we ready to move onto the next? So, copper gluconate, this is a draft report on the safety assessment of copper gluconate and it's the first time we're reviewing this. The Panel had previously reviewed the safety of gluconic acid, potassium gluconate, and sodium gluconate in 2019 with a published conclusion of safe as used. Additionally, several QSAR models were described by the European Chemicals Agency dossiers for these endpoints, and they've been included in this report the CIR's performed an exposure assessment which has been referenced in many of the other discussions we've had in this section.

We acknowledge the second wave data and I think we agree with those suggestions, but we'll discuss them. This functions in cosmetics as a skin conditioning agent. The ingredients are generally regarded as safe so they GRAS as a direct human food ingredient. We have method of manufacturing and impurities. We have 2023 VCRP data of copper gluconate being used in 170 reported uses with 140 as leave on. And we have maximum concentration of 0.2 percent in baby shampoo and 0.006 percent in an eyeliner near the eye and we have a QSAR model.

So, I'll just open it up for discussion. Who wants to start? Tom, you want to lead us?

DR. SLAGA: Yeah. Very nice summary. Obviously, related compounds other salts of gluconate were found safe, and this particular copper version is GRAS. It's found in food -- put in foods for protection and also, we have, some data also supporting that it's -- number one, it's not genotoxic and I have some concerns about use with babies and around the eyes and I

would assume that it's really not an irritant to the eye, hopefully. Overall, I could push to go for safe as used based on even some of the calculations in the report.

DR. COHEN: I will round the bend and then reopen to discussion. David?

DR. ROSS: Yeah. I mean, it's quite interesting the highest concentration -- getting back to our comments about highest concentration but the max concentration was baby shampoo which I think is a little bit unusual for us. I found the exposure assessment very helpful and persuasive. The RDAs, adults and babies were 900 and 340 micrograms per day respectively. I think we're getting up to a body lotion exposure of about 70 micrograms. It's orders of magnitude less than the RFD, so I think that was leading me towards what Tom was saying is safe as used in present practices.

I think the major issue are these predictive QSARs for the NOAELs which we talked about in the previous two documents. It's particularly a concern for dermal and ocular where we have no data whatsoever. And I'd like to see -- I guess in a perfect world I would've liked to have seen some data of a molecular nature on ocular and dermal, skin cells, or corneal cells or something like that which gives us a little bit of reassurance, and a bit more confidence in these endpoints.

The RDA issue gives us a lot of confidence but what do we know about potential skin and ocular irritation. So, I wanted your comments on that, particularly David and Wilma.

DR. COHEN: Yeah.

DR. BERGFELD: The GRAS.

DR. COHEN: Susan, why don't you make your comments and then we'll come around and process everyone's statements.

DR. TILTON: Okay. So, I agree with Tom and David. I mean, in terms of the QSAR predictions, so those for repeat dose and reproductive and developmental. There was other toxicity data; there were other DART studies in which there weren't significant effects observed for reproductive effects and developmental endpoints and offspring. So, the QSAR predictions were pretty consistent with the other data that was being presented.

Unfortunately, as David mentioned there really were no other irritation or sensitization studies to rely on and the predictions ranged into the moderate and mild irritation, particularly around the eye. I think we're early enough with this report that we could request other dermal irritation or sensitization studies and see if there's data out there.

I mean, I tentatively agree, though, with safe as used.

DR. COHEN: So, the one issue to me is the irritation/sensitization and copper is a known sensitizer topically. It does have some correlation with nickel allergy which is the most common patch tested allergen probably in the world. And there is data on contact dermatitis to copper and there's data on patch testing down to 0.2 percent eliciting positive patch tests. To me, it wasn't the gluconate; it was the metal. The metals in contact dermatitis are always the issue and so I think we go for an IDA for irritation and sensitization at max concentration.

DR. ROSS: Yeah, I agree with that. I feel better with having some data to back that up rather than just the predictive NOAELs.

DR. COHEN: Yeah. We have, really nothing in human skin here that -- and there's plenty of reports out there, right, and I'll include them in my data feedback. But there's at least two articles I pulled. One from 2014, one from 2001 that goes through copper hypersensitivity reactions. They're in IUDs and have caused issues in some people. So, there's enough out there that we should ask for this. It's a rare sensitizer but it's well described.

DR. ROSS: I think I pulled the same papers. They described them as a weak sensitizer relative to the metals but (audio skip).

DR. COHEN: Right. And it's not like the, I mean, often the patch testing concentrations are two and five percent, but one of the studies took copper sensitive patients and patch tested them down to 0.2 percent and in some people, they were able to elicit reactions. So, it's not like -- we're right where the max uses in the baby shampoo, right? So, I think it behooves us to have that.

DR. EISENMANN: So, if I'm hearing you correctly, you're okay with data on other copper compounds on sensitization and irritation, correct? But I don't think they patch test with copper gluconate, they'd probably use copper sulfate or something like that.

DR. COHEN: Yes.

DR. EISENMANN: Okay.

DR. COHEN: Yes, but so the question is, I ran into the same issue in my head. Right, it's usually copper sulfate. There might've been one other one. But the question is I'm not sure, maybe Susan you'd know, of the valances for copper differ in copper sulfate than copper gluconate, because the valance of the metal is going to make a difference.

DR. ROSS: (Audio skip) copper gluconate and copper sulfate, they should be plus two not plus one.

DR. TILTON: Yeah, I would agree.

DR. COHEN: I think copper sulfate can exist in two different forms, right?

DR. ROSS: Copper can, it's plus two and a plus one. Yeah. Copper can.

DR. COHEN: Yeah. So, if copper sulfate can be a plus two and copper gluconate's a plus two then, yeah, I think we can -- I mean, the Belsito team might have a different opinion about it but usually it's the valence of the metal that's been predicting sensitivity like hexavalent chromium being very sensitizing. We've trivalent chromium not very sensitizing. So, if we're in the same valence state, yeah, I'd still like to see something. I'm open to hearing more. But just because they didn't patch test to it doesn't mean -- it's just the most readily available thing that they had.

DR. ROSS: I'm not sure about the valence argument, but I think they certainly need more. I agree with you.

DR. COHEN: Any other discussions on it? Wilma, did you have any other?

DR. BERGFELD: No, I thought that was good discussion and there's no reason not to call for the -- I think you want human, though, if you can get it, don't you, for irritation and sensitization?

DR. COHEN: Yeah, HRIPT.

DR. BERGFELD: Mm-hmm.

DR. ROSS: I mean, with the eye, you could ask for a molecular -- you can ask for corneal cells or whatever.

DR. COHEN: And an eye. Okay.

DR. ROSS: We had a few (audio skip) dossiers, human corneal cells that were used that'd be skin, I think, that were used in those.

DR. COHEN: Right. And if the HRIPT isn't showing any signaling even early on from those assaults then that gives us a little bit extra if we have non in vivo assessment like the corneal cells. Okay, we can move on to t-Butyl Alcohol?

Full Panel – March 29, 2024

DR. BELSITO: This is the first time that we're looking at this safety assessment. The SLR was announced in December of 2023. We previously reviewed the safety of gluconic acid, potassium gluconate, and sodium gluconate in 2019. Final Report was published with a conclusion that those ingredients were safe in the present practices of use and concentration in cosmetic described in this report.

Copper as we all know is an essential element, so much of the systemic toxicity or all of the systemic toxicity was really pretty much cleared by that. However, we only received information on the impurities on food-grade copper, so we don't have information on the impurities that might be present in copper gluconate. Nor do we have dermal irritation and sensitization or ocular irritation at concentrations of use. So, while we thought the systemic endpoints were okay, we're going out with insufficient for impurities, dermal irritation and sensitization at concentration of use, and ocular irritation if available.

DR. BERGFELD: Is there a second or a comment?

DR. COHEN: Second.

DR. BERGFELD: Any comment?

DR. COHEN: And Don had perfectly reviewed our needs.

DR. BERGFELD: Any comment about the copper sensitization? And, we're going to wait.

DR. COHEN: Well, that's why we're asking for irritation and sensitization, then, you know, Don, there's plenty of reports of copper contact dermatitis and even patch testing down to max use in sensitized people. But, that's neither here or there, we got the IDA out.

DR. BERGFELD: Okay. So it's been proposed and the comments have been made on presenting this as an IDA with the insufficiencies as noted. Those against? Abstaining? Unanimously approved to send this out as an IDA with the impurities and irritation, and sensitivities and ocular concerns data request. Okay, moving on to *t*-Butyl Alcohol, Dr. Cohen.

SEPTEMBER 2024 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – September 30, 2024

DR. BELSITO: So, this is the second time we're looking at the safety assessment. March 2024, we issued an IDA with the following data needs: impurity data as used in cosmetics, dermal irritation and sensitization data at maximum concentration of use, ocular irritation data if available. We had numerous data submissions in response. They've been incorporated into the report. And what do we think? So, we have 0.008 percent on leave-on and 0.36 percent in oral hygiene.

DR. SNYDER: Point zero, zero, zero, eight in baby products.

DR. BELSITO: Right. And the question here as to how does oral hygiene fit in. Where is this? I guess daily exposure from food use would be much -- would result in much larger systemic exposure than those from using cosmetic products. Oh, no, how does oral hygiene fit in? The ingredient functions in cosmetics as a skin conditioning agent, so why is it used in an oral hygiene product, to condition the gums?

MS. FIUME: You don't want to ask Bart that question. Skin conditioning agent is a catchall for everything.

DR. SNYDER: Yeah.

MS. FIUME: So, the functions aren't vetted necessarily, is that correct, Kim? The functions aren't vetted. They're just -- yeah. So --

DR. BELSITO: So, we don't really care. Okay. Then I answered this question, but didn't occur to me before with the systemic exposure. It was a condition called Wilson's disease, where copper ingestion can be --

DR. SNYDER: Toxic in the liver.

DR. BELSITO: -- toxic. And my question was, does the FDA require a label warning individuals with Wilson's disease, particularly given the oral hygiene use? And the answer to that is surprisingly no, even on copper supplements. So, I don't think we need to label it on a cosmetic. It's not on a supplement.

DR. KLAASSEN: I thought that in a document we should at least state that there is this disease in humans.

DR. BELSITO: Right.

DR. KLAASSEN: Well, there's actually two. There's the Wilson's disease and the Menkes disease, and it has to do with the copper transporters.

DR. BELSITO: Right.

DR. KLAASSEN: And not to make a big deal out of it, but I think if we don't -- we should at least state it that we are aware that there is such a thing.

DR. BELSITO: Where would we do that?

MS. BURNETT: I think before we've done it in the introduction.

MS. FIUME: That would give it too much weight I think.

MS. BURNETT: True.

MS. FIUME: It could be something under clinical -- maybe in the clinical section to say that you're aware. But I'm trying to think. We've done it recently. Priya's not on. One of Priya's report that had --

DR. BELSITO: I mean, it's not other relevant studies. It's a genetic defect, copper transport.

MS. BURNETT: So, I want to say we put some things somewhere in a MSG report, but I don't remember what. Because we recognize that some people have a condition.

MS. FIUME: It's not toxicokinetic, is it?

MS. BURNETT: I don't know.

MS. FIUME: What was the other? It was Wilson's and?

DR. KLAASSEN: Menkes, M-E-N-K-E-S.

MS. FIUME: Thank you.

DR. KLAASSEN: Has to do with transporter ATP7A.

MS. FIUME: So, would it belong under toxicokinetics?

DR. SNYDER: Could.

DR. KLAASSEN: It could, yeah. Yeah, that'd be the best place.

MS. FIUME: Okay.

DR. RETTIE: Yeah, the Wilson's disease is pretty rare.

DR. BELSITO: They're both pretty rare.

DR. SNYDER: Yeah.

DR. RETTIE: Is Menkes even rarer?

DR. SNYDER: Oh, way rarer. Menkes is way more -- lot more rare.

DR. KLAASSEN: It's not a big deal unless you have it.

DR. RETTIE: (Inaudible).

DR. BELSITO: Yeah.

DR. KLAASSEN: Menkes disease.

DR. RETTIE: Yeah. Had no idea.

MS. FIUME: So, just a brief mention just to acknowledge it --

DR. SNYDER: Yeah.

MS. FIUME: -- but no real details.

DR. SNYDER: Yeah.

MS. FIUME: Okay.

DR. BELSITO: No.

DR. KLAASSEN: Yeah, that's all I'm asking --

MS. FIUME: Okay.

DR. KLAASSEN: -- is that somebody reads this who is -- aren't aware of this.

DR. BELSITO: Yeah, I mean, that's why I looked into what does the FDA require because copper gluconate is a supplement that's out there. And do they require it to be labeled? And it's not on the labels.

DR. SNYDER: Surprising.

DR. BELSITO: It's not like (inaudible).

DR. RETTIE: The Menkes sufferers don't make it past 37.

DR. BELSITO: Yeah, but they can get copper when they're a teenager. God forbid they get a copper IUD. Anyway. So, yeah, mention it in toxicokinetics that we're aware of it, and then don't mention it again.

MS. FIUME: Sure.

DR. BELSITO: We can at least bring it up, see what the other group thinks, if they even raised the issue. Okay. Okay. Otherwise --

DR. SNYDER: Safe as used.

DR. BELSITO: Yeah, there was just a few.

MS. BURNETT: I see there's a draft discussion. Is there anything I can put in that or subtract from that?

DR. BELSITO: Yeah, I mean, we didn't -- did you mention the fact that we didn't have a lot of genotox data but that it's GRAS. Well, we had carcinogenicity.

MS. BURNETT: This wasn't my report, so just -- sorry.

MS. FIUME: The genotox is not mentioned in there.

MS. BURNETT: Mention genotox lack -- its lack of genotox.

DR. SNYDER: Yeah, we have genotox -- oh, no, we have lack of genotox, but we have carcinogenicity.

DR. BELSITO: Carcinogenicity.

DR. SNYDER: Yeah.

DR. KLAASSEN: In this article a number of places, it talks about structure activity relationship half a dozen times. And Dan Liebler, when he was on this committee, often said, "With metals, there is no structure activity relationship." I kind of agreed with him on that.

DR. RETTIE: Different valance states (inaudible).

DR. BELSITO: Yeah, I just put in the discussion: Discus hepatic carcinogenic effect and nephrotoxicity at levels much greater than cosmetic. And conclusion, safe as used.

DR. SNYDER: Yeah.

DR. BELSITO: And we have GRAS status for it as well.

DR. KLAASSEN: Correct. It's essential.

DR. RETTIE: I'd argue with Dan on that for chromium, right? It's only chromium-6 that's toxic, is that right?

DR. KLAASSEN: Yeah.

DR. BELSITO: Heavy metals boilerplate.

DR. RETTIE: Pushing the definition of (inaudible).

DR. BELSITO: So, heavy metals, carcinogenicity, and nephrotoxicity at doses much larger than exposure to cosmetics, GRAS status. Everything else I think is --

MS. FIUME: Does anything need to be said further about the sensitization in the discussion because -- oh, no, there's a powder 0.1 percent. Okay. I only saw the really low dose at first.

DR. BELSITO: Okay. Anything else?

Cohen Team – September 30, 2024

DR. COHEN: Okay. Copper gluconate. This is a draft tentative report for copper gluconate. This is the second time we're seeing this. At the March 2024 meeting, the Panel issued an insufficient data announcement and identified the following data needs. Impurities for copper gluconate, dermal irritation and sensitization at max use, ocular irritation if available. According to the 2023 VCRP, copper gluconate has 170 report uses, 140 of which are leave-on products. The survey conducted by the Council shows leave-on formulation of 0.008 percent in non-spray night products and a max reported concentration of 0.36 in oral hygiene products.

There's some lipstick uses. It would appear in this new report we received impurity data; we have good sensitization and irritation data. We have some ocular irritation data. Thoughts from the group?

DR. TILTON: So, we've pretty much received all of the requested data on impurities, dermal irritation and sensitization, and ocular irritation with regards to impurities. So, this can be a clarification that someone can answer, but my understanding is the copper gluconate powder for use in cosmetics is food grade, and so the impurities reported were for food grade powder at approximately a hundred percent with none of the tested elements present above a typical threshold amount. So, I didn't have any concern about the impurities.

DR. COHEN: David?

DR. ROSS: Yes, I think previously we didn't have too many concerns. We went out with the IDA, and I think as Susan nicely pointed out, we've got HRIPTs no less -- HRIPTs, ocular, and impurity data. But I did have some comments here. Our maximum concentrations of use have been changed quite a lot in this document. Previously it was a little unusual that the maximum concentration of use of previous iteration was a baby product.

DR. COHEN: Is a what?

DR. ROSS: Was a baby product. It was a product used for babies and that's changed. Actually, quite pleased to see that. But there's a max concentration now, David as you pointed out, was 0.36 percent in mouthwash, 0.1 percent dermal, eye liner and I think baby shampoo was something like eight points times ten to the minus one, two, three, four -- ten to the minus five percent. So that's changed. I did want to point out that one of the HRIPTs we've received, an important one which we got at 0.2 percent, that's -- we have a maximum dermal of 0.1 percent.

But that rinse off product was actually a baby product and so we now actually have a maximum concentration in baby products of 0.00008 percent and so we're quoting a two percent HRIPT using a baby product. I just think we have to make it clear that that's not -- that's a historical --

DR. COHEN: Yeah, we've come across this where we have data that have higher concentrations of use in the HRIPT, but that was my first year, I couldn't wrap my head around it. But sometimes it's just the start products that are used, right, they're not necessarily used now.

DR. HELDRETH: Yeah, well, and test articles are not always consumer products. You know, someone may make a pre-formulation for testing purposes. It may go on the market; it may come off the market, it may have never went off the market.

DR. ROSS: Well, could we make that into a real clarification, historical or whatever, and that would be really useful I think because otherwise it's contradictory and I think --

DR. COHEN: It's not contradictory --

DR. ROSS: Well, it was to me.

DR. COHEN: -- in that the sensitization table talks about the products that were tested, but the use tables are clear.

DR. ROSS: Correct. Correct, no, I agree but it is -- let me amend my statement. It's not contradictory, but it needs clarification.

DR. BERGFELD: You could put it in the summary though. You could put they were tested at higher concentrations, but the use is lower.

DR. COHEN: To David's point, there's a very tricky nuance here and the nuances/our conclusions are safe as used in present practices and concentrations described in this report. Well, guess what, 0.2 in a baby product is in the reports.

DR. ROSS: Exactly.

DR. COHEN: So, I do think that needs clarification. Because why can't someone look at that and say, looks like 0.2s in the reports, it's in the table there, it's clear as day. Why can't we use that in our baby product?

DR. HELDRETH: Yeah. We can make that clear that that, that's not the current concentration and practices of use.

DR. ROSS: Yeah, I think that'll be fine, Bart. Thank you. I think it's an editorial point.

DR. COHEN: It's come up before and I've never remembered how we reconciled it. I think we bring that up.

DR. ROSS: So that was the first point. I've got three. Three seems to be my magic number on these documents this morning. So, ocular, as Susan pointed out, we got that. It was an EpiOcular human cell construct, which is a nice 3D model and it's OECD approved. The minimal tox there, MTT, was at 0.0025 percent. Our max ocular use in these revised concentrations it's a little higher than that at 0.006 percent. So, if you were just going on that you can't quite get to that percentage, but you also have QSAR and that predicted this to be a potential mild irritant only, which I'm find with combinations, and I think you can be fine with that.

DR. COHEN: We'll go out as safe as used?

DR. ROSS: At that one, yeah. Impurity data was okay. Sorry, I actually have four points on this one. I have to step back. The fourth one is the exposure assessments in here I thought was very helpful and persuasive. And I said that last time and I'll say it again because it's really, really, very good. The RDA for adults was 900 micrograms, for babies it was 340 micrograms.

My point here is that previously we had included a calculation for the baby product, if you remember previously, that was our maximum exposure. And that was done with the VERMEER calculation, Bart, by Jinqui I think. And even though we've gone way, way, way, way back on the concentration you used in baby products, I'd still like to see that VERMEER calculation. I mean it's going to be very, very low, but I would just like the document to highlight that we actually did it on the baby product because we had the possibility of doing it.

DR. BERGFELD: And you would put it here under this MOE?

DR. ROSS: Wherever he put the exposures at. Was it a table, I think, Bart, maybe? I'd have to --

DR. COHEN: It's an exposure assessment on PDF 24.

DR. ROSS: Yeah. Let me look. You said 24, David, is that --

DR. COHEN: Hold on. Yeah.

DR. ROSS: Yeah. So, it would go in there. It would go in there as another calculation. It would just be added onto the existing ones. I mean, you don't have to do that because the concentration's pretty darn low. It was in last time and it gave me some comfort to see that in there and I prefer to see that in there.

DR. COHEN: So, this is a -- hold on -- draft tentative report. So, we're getting another crack at this, right, Bart?

DR. HELDRETH: That's correct.

DR. ROSS: Do you need another crack at it?

DR. COHEN: Well, you're asking for that data to go with it.

DR. BERGFELD: It's editorial.

DR. ROSS: It's editorial. It was in previously and we know it was fine.

DR. COHEN: So, we'll see it, right? We're going to see it, next time. It will come back, right?

DR. BERGFELD: For final.

DR. ROSS: It will come back for final?

DR. BERGFELD: Yeah, it always does. It goes out for 60 days and comes back.

DR. COHEN: This is a tentative document. We're going to see it next time as a final. It may come back fast, right?

DR. ROSS: It should, yeah.

DR. HELDRETH: Well, it'll go out as a tentative report for a 60-day comment period, which makes it unlikely to come back right away in the summer, just so that we have that window.

DR. COHEN: So, maybe March?

DR. HELDRETH: But probably March it would come back down final report.

DR. COHEN: Yeah, okay.

DR. TILTON: Still in my notes I also noted the ocular irritation data at 0.0025 percent, not too far below the max use. So, there were no signs of irritation, and we have QSAR also not seeing -- really no concerns with irritation or sensitization dermally, so I didn't have any concerns about that. With regard to the note about 0.2 percent testing in the HRIPT it was mentioned that it was in a baby product formulation.

I mean, we can make note that that is higher than what is in the products reported. I mean, when we report safe as used at practice and concentration of use, I would never -- I mean there's lots of concentrations used for testing in the document that are much, much higher across all the different kinds of testing that are done. I don't think any of those would suggest that the products could be used at those concentrations.

So, I've never interpreted that way. I've always interpreted that it's in the table as how the products are currently used on the market, but I'm okay with making that clarification since it's with regard to a baby products and the HRIPT in human subjects. But I've never had that confusion.

DR. COHEN: I think it's a good point because it's in present practices -- present practices of concentration and use and that says as described in this report. So, I think maybe some boilerplate language should just be that it's based on concentration of use tables and not on anything else in the report.

DR. HELDRETH: Yeah. Often when I go and present to them about how a formulator or even a person of the public can use the CIR report, what does all of that alphabet soup mean after it says safe. I'm always pointing people, well, go and look at the use table, check out the category. If it's in a nail product, go look in the nail category for the maximum reported concentration there and that's the limit where the panel's conclusion applies to. It's not necessarily unsafe after that, it's just (inaudible) applied.

But I've often thought it wouldn't hurt to have some verbiage in the reports that explains that so that people don't have to wait until I show up at their conference and explain that part. It's something that we can put in our introduction or some boilerplate --

DR. COHEN: I think that makes a lot of sense.

DR. HELDRETH: -- when we say present practices of use and concentration, see Table 1.

DR. ROSS: That's fine.

DR. TILTON: Yeah, just reference the table.

DR. ROSS: So, you're not going to clarify this with respect to the baby product?

DR. COHEN: No, we're going to clarify it.

DR. ROSS: Okay, good.

DR. COHEN: I think that's the comment -- that's editorial. We'll clarify it. So, maybe that could be this one because it's a tentative report, we would see that in the draft final, and maybe we can evaluate that verbiage going forward.

DR. HELDRETH: And make it across the board --

DR. COHEN: Yeah.

DR. HELDRETH: -- if anybody wants it.

DR. COHEN: Okay. We can exit copper.

Full Panel – October 1, 2024

DR. COHEN: Okay. So this is a draft tentative report for the safety assessment of Copper Gluconate. This is our second time at it. In March, the Panel issued an insufficient data announcement identifying the following data needs, impurities, dermal irritation and sensitization and max use, ocular irritation if available. We felt that the report was updated and had fulfilled our data needs, and we will continue with a motion of safe as used.

DR. BELSITO: Second.

DR. BERGFELD: Second? Any other comments regarding this document, Dr. Belsito?

DR. BELSITO: Yeah. We just thought that, in the toxicokinetic section, at some point it should be mentioned about patients with Wilson's and Lenke's disease who are sensitive to Copper because of lack of appropriate enzymes. I did look up just to see what kind of labeling might be required for Copper supplementation, and there's none requiring a mention of individuals with Lenke's or Wilson's disease.

DR. BERGFELD: Well, as we know, that's very rare, but yes.

DR. BELSITO: Very rare.

DR. ROSS: I had a couple of comments on --

DR. BERGFELD: Oh, please proceed.

DR. ROSS: -- the baby product.

DR. COHEN: Yeah. I was gonna -- go ahead.

DR. ROSS: Yeah. One of the HRIPTs we got was 0.2 percent, which was actually a baby product. And our maximum concentration of use for baby products in this dossier has been amended previously. In the previous version, that was the maximum concentration of use. It was a baby product. But it's now been amended in this dossier. It's something like 0.00008 percent. So, it's pretty low in baby products. But we have an HRIPT in there of 0.2 percent.

So, we asked could there be some clarification that that was a historical product? Or whatever the case was that we got to that point, could we clarify that that was no longer being used as a baby product in some way? So, that was one issue. And then, the second issue was the -- David, do you want to comment on that? Is that what you're trying to do?

DR. COHEN: Yeah. Well, if you're moving on to another comment, maybe I'll comment on this one at hand. This has come up a number of times over the years, where we have max use concentration that's clear in the use table. But then, in our HRIPT and other parts of the dossier, there are products that we tested at much higher concentrations.

And, you know, there's an assumption that they're not being used now or that that product was just being used for irritation and sensitization. After the meeting, I thought maybe for all of our reports we could have something such as safe in cosmetics in present practices of use and concentration described in the safety assessment, refers exclusively to the concentrations detailed in the use tables, not concentrations of dosages mentioned elsewhere in the report.

DR. BERGFELD: You wanted that in the conclusion or in the discussion?

DR. COHEN: It could be in the conclusion or it could be up high when we state our finding, but it could be anywhere. Maybe the conclusion is not a bad place for it.

DR. HELDRETH: Might fit in really well in the Cosmetic Use section.

DR. COHEN: Yeah. It's gonna be in --

DR. BELSITO: And I think I would not want it in the conclusion. I mean, I think it can be in the Cosmetic Use section or in the end in the discussion if you really wanted to hammer it in.

DR. HELDRETH: Yeah.

DR. COHEN: I'm okay with either one of those or both.

DR. HELDRETH: Yeah. I think Don makes a good point. Whenever I go out and I'm presenting the results of the Panel and trying to explain what safe as used, and then all of the other verbiage after that, and what that all means, it's often a surprise to folks it means that that, "in present practices of use and concentration," means go look at the Use Table, look at the category, look at the maximum concentration. And those are the limits of the Panel's conclusion. So, yeah, putting that into the report, maybe fewer people will be surprised.

DR. BERGFELD: I think that's a great addition. And I think that we should, in some way, look to do that in multiple ingredients going forward.

DR. HELDRETH: Yeah. And we could put it in every one.

DR. BERGFELD: Yeah.

DR. BELSITO: As a standard.

DR. COHEN: Put that in all of them.

DR. BERGFELD: Yeah, yeah. All right. Any other comments?

DR. ROSS: Do we just want to -- sorry I --

DR. BERGFELD: You had a second.

DR. ROSS: The baby product, and this is not something we have to do. But the previous version, you know, when the maximum concentration of use was actually the baby product in there, we had a calculated exposure using the in silico tools using that baby product because it was at maximum. You know, that was on max use.

And I'm just wondering whether or not we should keep an estimate of exposure to the baby product, even though the concentration has gone way down. It does show that we're sensitive, no pun intended, to looking at baby products. And that could be a worthwhile addition. But I'm fine either way, whatever the Panel wants to do. You know, if we don't need it, don't do it. But at least I felt we should discuss it.

DR. BERGFELD: Allan?

DR. BELSITO: Well, there's not a tox endpoint that we're concerned about, really.

DR. ROSS: No. No, there is not. You are correct. Yeah. Okay. I'll retract that, and you can move forward with that.

DR. BERGFELD: Okay. All right.

DR. BELSITO: And in the discussion (inaudible) mention of heavy metals. I used our heavy metal boilerplate.

DR. BERGFELD: Okay. All right. Anything else to be added to this or changed or edited? Nothing. Call the question. All those in favor of safe for this ingredient, Copper. Unanimous. Okay.

DR. COHEN: Aye.

DR. BERGFELD: Good.

Safety Assessment of Copper Gluconate as Used in Cosmetics

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ABBREVIATIONS

ALT	alanine aminotransferase
APP	amyloid precursor protein
AUC	area-under-the-curve
BBN	*N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine
CAS	Chemical Abstracts Service
c-fos	protein c-Fos
CIR	Cosmetic Ingredient Review
CLP	Classification, Labelling, and Packaging regulation
C_{max}	concentration maximum
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
CTR1	copper transporter 1
DEN	*N*-nitrosodiethylamine
DHPN	2,2'-dihydroxy-di-*n*-propylnitrosamine
Dictionary	web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI)
DMH	1,2-dimethylhydrazine
DMSO	dimethyl sulfoxide
DMT1	divalent metal transporter 1
DNA	deoxyribonucleic acid
ECHA	European Chemicals Agency
EC3	effective concentration to induce a 3-fold increase in local lymph node proliferative activity
EPA	Environmental Protection Agency
ET_{50}	time for the test article to reduce the viability of the skin to 50%
EU	European Union
FDA	Food and Drug Administration
Gadd45α	growth arrest and DNA damage inducible alpha
GGT	gamma glutamyl transpeptidase
GHS	Globally Harmonized System
GRAS	generally recognized as safe
GST-P	glutathione S-transferase placental form
HGF	hepatocyte growth factor
HRIPT	human repeated insult patch test
IL-1α	interleukin 1-alpha
INCHEM	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
Ki67	protein biomarker for cell proliferation
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect-level
MMAS	modified maximum average score
MNU	*N*-methylnitrosourea
MRL	minimal risk level
mRNA	messenger RNA
MT1	metallothionein 1
MT1a	metallothionein 1a
MT2a	metallothionein 2a
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NA	not applicable
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NOAEL	no-observed-adverse-effect-level
Nos2	nitric oxide synthase
NoG	Notes of Guidance
NR	not reported
OECD	Organisation for Economic Co-operation and Development
OPPTS	Office of Prevention, Pesticides, and Toxic Substances
p21	tumor protein p21
p53	tumor protein p53
Panel	Expert Panel for Cosmetic Ingredient Safety
PDII	primary dermal irritation index
QSAR	quantitative-structure activity relationship
RDA	recommended daily allowance
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals
SCCS	Scientific Committee on Consumer Safety

SED	systemic exposure dose
STOT RE	specific target organ toxicity, repeated exposure
$t_{1/2}$	half-life
TG	test guideline
TGFβ	transforming growth factor-β
TNF-α	tumor necrosis factor alpha
TUL	tolerable upper limit
US	United States
USP	US Pharmacopeia
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Copper Gluconate, which is reported to function in cosmetics as a skin-conditioning agent. Industry should minimize impurities, such as heavy metals, according to limits set by the US Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA). The Panel reviewed all available relevant data to determine the safety of this ingredient and concluded that Copper Gluconate is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This assessment reviews the safety of Copper Gluconate as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), this ingredient is reported to function in cosmetics as a skin-conditioning agent.[1]

In 2019, the Panel published a final report that reviewed the safety of gluconic acid, potassium gluconate, and sodium gluconate, with the conclusion that these ingredients are safe in the present practices of use and concentration in cosmetics described in the safety assessment.[2] The full report can be accessed on the Cosmetic Ingredient Review (CIR) website: (https://cir-reports.cir-safety.org/).

Copper Gluconate is generally recognized as safe (GRAS) as a direct human food ingredient and as a nutrient or dietary supplement used in animal drugs, feeds, and related products; hence, daily exposure from food use would result in much larger systemic exposures than those from use in cosmetic products. The Panel has noted that copper is an essential nutrient. Thus, the primary focus of the safety assessment of this ingredient as used in cosmetics is on the potential for local effects from topical exposure.

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 extensive search of the world's literature; a search was last conducted August 2024. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) 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

Copper Gluconate (CAS No. 527-09-3) is the copper salt of gluconic acid that conforms to the structure depicted in Figure 1.[1]

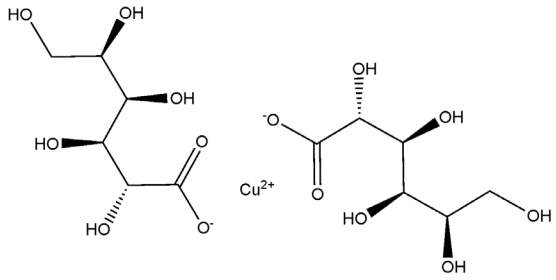

Figure 1. Copper Gluconate

Chemical Properties

Copper Gluconate is a light blue to bluish-green or green solid or crystalline, odorless powder that has a formula weight of 453.9 g/mol (compared to 63.55 g/mol atomic weight of copper) and an estimated log K_{ow} of - 2.98.[3-7] Additionally, Copper Gluconate has a density of 1.78 g/ml and is soluble in water; although slightly soluble in alcohol, it is insoluble in acetone, ether, and other organic solvents. The chemical properties of Copper Gluconate are further outlined in Table 1.

Method of Manufacture

The following are general methods of manufacture, and it is unknown whether these are utilized in the manufacture of Copper Gluconate as a cosmetic ingredient. In one method, a 1.0 M aqueous solution (6 ml) of gluconic acid (0.006 mol) is added to a suspension of copper hydroxide (0.003 mol) in 5 ml of distilled water.[5] The mixture is stirred at 75°C and monitored by infrared spectroscopy; the reaction is conducted until the absorption band for the carboxylic group of gluconic acid is no longer

detectable. The solvent is evaporated on a rotary evaporator at 65 - 75°C, at a residual pressure of 10 - 20 mmHg, and the resulting residue is dried in a desiccator. According to 21CFR184.1260, Copper Gluconate is prepared by reacting gluconic acid solutions with cupric oxide or basic cupric carbonate.

Impurities

According to a supplier, specifications for food-grade Copper Gluconate powder included 98 – 102 % purity, with a 1% maximum limit for reducing substances.[7,8] Results from a certificate of analysis for a food-grade, US Pharmacopeia (USP) Copper Gluconate powder demonstrated a purity of 100.2%, copper content of 14%, reducing substances content of 0.21%, < 0.07% chloride and < 0.05% sulfate (both below maximum limits), 0.10 ppm arsenic (3 ppm maximum limit), 0.02 ppm lead (5 ppm maximum limit), a lack of coliform presence, and aerobic plate count and yeast and mold counts that were below specification limits (< 1000 cfu/g and < 100 cfu/g, respectively).[7,9] In an elemental impurity analysis of a USP Copper Gluconate powder, none of the tested elements were present above typical threshold values.[10] According to specifications provided by another supplier, the presence of cadmium, chromium, mercury, selenium, and thallium (each < 0.1 ppm), arsenic, cobalt, lithium, molybdenum, and vanadium (each < 1 ppm), antimony, barium, and lead (each < 2 ppm), and nickel (< 5 ppm) in Copper Gluconate would be unlikely and minimal.[11] Additionally, specifications for food-grade Copper Gluconate include an acceptance criteria of no more than 5 mg/kg lead in a 1 g sample of Copper Gluconate.[8]

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. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was terminated in 2023, and as of 2024, manufacturers and processors have been mandated to register and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses, which are exempt from MoCRA reporting for most cosmetic product categories. However, to utilize the exemption, the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 h.[12] Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting). Although the VCRP program is now defunct, trends in frequency of use from the RLD alone are not yet possible in that a baseline is currently not available.

According to RLD that CIR received in 2024, Copper Gluconate is used in 666 formulations, with the majority of the uses (492) in skin care preparations (Table 2).[13] VCRP survey data received in 2023 reported Copper Gluconate to be used in 170 formulations, 140 of which are in leave-on formulations.[14] The results of the concentration of use survey conducted by the Council in 2022 and updated in 2024 indicate that the maximum reported concentration of use for Copper Gluconate in a leave-on formulation is 0.008% in non-spray night products; overall, the highest maximum reported concentration of use is 0.36% in other oral hygiene products.[15]

Several uses in products applied near the eye (at up to 0.006% in eyeliners) and in products that can result in incidental ingestion have been reported (e.g., it has reported uses in mouthwashes and breath fresheners (no concentration reported), “other” oral hygiene products (0.36%), and lipsticks and lip glosses (no concentrations reported)). Copper Gluconate is reported to be used in baby shampoos and baby lotions, oils, powders, or creams at a maximum of 0.00008%.

Copper Gluconate is also reported to be used in face powder formulations (concentration not provided) and could possibly be inhaled. In practice, as stated in the Panel’s respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetics would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

Some products containing Copper Gluconate may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined by the FDA, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available in some instances. None of the reported product categories for this ingredient as listed in the RLD include a designation using airbrush application, so it is possible that this ingredient is used with airbrush delivery systems, but not reported as such. Additionally, the Council currently surveys the cosmetic industry for maximum reported use concentrations of ingredients in products which may be used in conjunction with an airbrush delivery system; thus, this type of data may also be available when submitted. Please note that no concentration of use data were provided indicating airbrush application. Nevertheless, no consumer

habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

Copper Gluconate is not restricted from use in any way under the rules governing cosmetic products in the European Union (EU).[16]

Non-Cosmetic

According to the US National Institutes of Health Office of Dietary Supplements, copper is an essential mineral which is naturally present in the human body and in some foods; 900 µg is the recommended daily allowance (RDA) for adult copper intake.[17] The tolerable upper limit (TUL) for copper intake is 10,000 µg/d.[18]

As indicated in 21CFR184.1260, Copper Gluconate is affirmed as GRAS by the US FDA as a direct human food ingredient, which includes use in nutrient supplements and in infant formula, provided that levels do not exceed current good manufacturing practices. In addition, Copper Gluconate is also considered GRAS as a nutrient or dietary supplement used in animal drugs, feeds, and related products at a level not to exceed 0.005% (21CFR582.5260) and as a trace mineral added to animal feed (21CFR582.80), both in accordance with good manufacturing or feeding practices. According to 21CFR310.545, Copper Gluconate has been present as an active ingredient in over-the-counter drug products for weight control; however, based on the currently available evidence, there is inadequate data to establish the safety or effectiveness of this use.

In the EU, copper and Copper Gluconate are categorized as mineral substances in Annex II of vitamin formulations and mineral substances which may be added to foods[19] and as minerals in Annex II of vitamin and mineral substances which may be used in the manufacture of food supplements;[20] listing in Annex II indicates the approved form for use in foods and food supplements. Additionally, Copper Gluconate is categorized as a mineral and is allowed in all 4 categories of food intended for infants and young children (i.e., infant formula and follow on formula; processed cereal-based food and baby food; food for special medical purposes; and total diet replacement for weight control).[21]

TOXICOKINETIC STUDIES

Animal

Oral

Groups of 449-d-old male C57BL/6J mice (5/group) were administered 0.005 M Copper Gluconate in drinking water for 92 d.[22] The accumulation of copper (dry weight) in the liver, kidney, brain, and heart of the test animals was compared to that of controls (drinking water). There was a statistically significant increase in copper accumulation in the livers of Copper Gluconate-fed mice, compared to controls (28.6 vs. 13.5 ng/mg). Differences between the amount of copper found in the kidney, brain, and heart of Copper Gluconate-fed mice and control mice were not statistically significant. In a related study, groups of 5 – 7 male C57BL/6J mice were administered 0.005 M Copper Gluconate in drinking water for 104 d, starting from various ages (64, 302, and 540 d of age). The accumulation of copper (dry weight) in the liver and kidney of Copper Gluconate-fed mice and controls (drinking water) was compared at the end of the experiment. The difference between copper accumulation in the liver of Copper Gluconate-fed mice and control mice was statistically significant in all 3 age groups; no statistically significant differences were observed in the amount of copper found in the kidneys of Copper Gluconate-fed mice (in all 3 age groups) compared to controls.

In a biodistribution study of copper (administered as Copper Gluconate), male Wistar rats (total number not specified) received a single dose of 79.5 mg/kg Copper Gluconate, dissolved in deionized water, via gavage, and were observed for up to 168 h prior to necropsy (rats were killed at 0.08, 0.17, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 12, 24, 48, 72, and 168 h).[23] Blood samples, brain tissue (striatum and midbrain), and liver samples were collected at each time point (n = 4 – 6). Controls received deionized water and were killed immediately after treatment; copper concentration in control blood and tissue samples was considered baseline. A plasma copper concentration maximum (C_{max}) value of 1.94 ±0.28 µg/ml was observed 1.5 h post-treatment, which was 73.1% higher than the baseline concentration ($p < 0.01$). Copper plasma concentration returned to baseline 72 h after treatment and the half-life ($t_{1/2}$)and area-under-the-curve (AUC) values were about 1.79 h and 2.48 ± 0.36 µg/ml*h, respectively. The C_{max} for copper distribution in the striatum tissue of Copper Gluconate-treated rats was 2.93 ± 0.21 µg copper/g of wet tissue at 0.25 h post-treatment (49.9% higher than baseline values) which returned to baseline after 168 h. A 27.6% increase in copper concentration (3.87 ± 0.25 µg copper/g of wet tissue) was observed in the midbrain of treated rats at 0.25 h post-treatment, however, no significant differences in copper concentration in the midbrain tissue of treated and control rats were observed. The C_{max} of copper in the liver of Copper Gluconate-treated rats was arrived at 12 h post-administration and was 391% higher than baseline (23.25 ± 1.75 vs. 4.735 ± 0.29 µg copper/g of wet tissue). Elimination or redistribution of copper found in the liver was observed 24 h post-administration. The area-under-the-curve $(AUC)_{0-168\,h}$ value for liver copper concentration was about 200 times greater than the AUC value for plasma copper concentration (494.8 ± 47.22 vs. 2.48 ± 0.36 µg/ml*h).

Human

Wilson's disease and Menkes disease are rare genetic defects characterized by abnormal copper metabolism in the human body.[24] Wilson's disease is a defect in copper excretion leading to progressive accumulation of toxic levels in the liver, brain, kidneys, and cornea. Menkes disease is a severe and fatal sex-linked mutation in genes coding for the copper-transport protein that results in copper deficiency in male infants.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Details on the acute oral and computational (dermal) toxicity studies on Copper Gluconate summarized below are found in Table 3.

In an acute oral administration study, male Wistar rats (4 - 6/group) were administered a single oral dose of 79.5, 156, or 312 mg/kg Copper Gluconate, in deionized water.[23] The survival rate of rats in the 312 mg/kg group was 31%. No animals from the 79.5 and 156 mg/kg groups died and no significant differences in weight gain or activity levels of the hepatic enzymes gamma glutamyl transpeptidase (GGT) or alanine aminotransferase (ALT) were observed 7 d after exposure compared to the control group. Male and female Wistar rats (5/sex/group) were administered a single dose of up to 3200 mg/kg Copper Gluconate, in water, in an acute oral toxicity study.[3] Five out of 10 of the animals from the 1800 mg/group died within 48 h of exposure, 8 out of 10 animals in the 2400 mg/group died within 48 h of exposure, and all 10 animals from the 3200 mg/kg group died within 24 h of exposure. The acute oral LD_{50} was determined to be 1709 mg/kg bw for both sexes. According to a quantitative structure-activity relationship (QSAR) model described in an ECHA dossier, the acute dermal LD_{50} for Copper Gluconate was predicted to be 2130 mg/kg bw in rats.[3]

Short-Term and Chronic Toxicity Studies

Details on the oral short-term and chronic toxicity studies and a computational study to predict short-term oral toxicity of Copper Gluconate summarized below are found in Table 4.

Groups of 5 male Fischer 344 rats were administered 0, 0.001, 0.03, or 0.6% (equivalent to 0, 10, 300, or 6000 ppm, respectively) Copper Gluconate in the diet for 2 wk, in a short-term oral toxicity study.[25] No differences in final body weight, liver weight, food consumption, or gross or histological changes in the liver were observed in the treated animals, compared to controls. Upon performing gene expression analysis in the liver, hepatic messenger RNA (mRNA) expression of metallothionein 1a (*Mt1a*; a metal metabolism-related gene) and growth arrest and DNA damage inducible alpha (*Gadd45α*; an apoptosis-related gene) were significantly increased in the 0.6% Copper Gluconate group and tumor protein p21 (*p21*; an apoptosis-related gene) expression was significantly increased in the 0.03 and 0.6% dose groups. Expression levels of tumor protein p53 (*p53*; an apoptosis-related gene) and inflammation-related genes, such as tumor necrosis factor alpha (*TNF*-α), interleukin 1-alpha *(IL*- 1α), nitric oxide synthase 2 (*Nos2*), and protein c-Fos (*c-fos*; a proto-oncogene) were not affected.

No adverse effects were noted in food consumption, body weight gain, urinalysis, or gross and microscopic examination of tissues and organs in male and female rats that were administered 0.006 or 0.06% Copper Gluconate (mean daily consumption of 3.46 or 34.9 mg/kg/d, respectively) in the diet for 24 wk.[26] Copper content was elevated in the kidneys of animals fed the diet containing 0.06% Copper Gluconate. In a chronic oral toxicity study, groups of 25 rats were administered 1.14% Copper Gluconate in the diet for up to 44 wk.[27,28] Significant growth retardation was discernible at 26 wk compared to controls, and over 80% of the animals died between week 17 and week 35. Upon necropsy, hypertrophied uteri, ovaries, seminal vesicles and hypertrophied stomachs, occasional ulcers, bloody mucus in the intestinal tract, and bronzed kidneys and livers were observed; chronic exposure to 1.14% Copper Gluconate in the diet was considered toxic. Groups of 6 male and 6 female Beagle dogs were administered 0.012, 0.06, or 0.24% Copper Gluconate in the diet (equivalent to 3, 15, or 60 mg/kg/d, respectively) for up to 1 yr.[27,28] Accumulation of copper was seen in the liver, kidneys, and spleen of animals in the 0.24% group; minimal liver function was observed in 1 out of 12 dogs in the 0.24% group after 1 yr of dosing, which was reversible within a 12-wk withdrawal period. No other test-article related effects were observed. Male C57BL/6J mice (number not specified) received 0.0005, 0.001, or 0.005 M Copper Gluconate in drinking water over the animal lifetime.[22] The survival curve and lifespan were significantly reduced by 11.8, 14.7 and 14.4% in the 0.0005, 0.001 and 0.005 M groups, respectively, indicating the absence of a dose-response relationship for survival. The effect of administering copper to adult Capuchin monkeys (2/sex; 7.5 mg/d) and copper as Copper Gluconate to young Capuchin monkeys (2/sex; 5.5 mg/d), in the diet, was evaluated in a 156-wk (3-yr) oral toxicity study.[29] No differences in food intake, body weight, or weight gain by age or time of exposure were observed in treated adult and young Capuchin monkeys, compared to age-matched controls. After 24 mo, Ki67 (a protein biomarker for cell proliferation) and MT1 (metallothionein 1) protein levels were significantly greater in the liver tissue of treated adult and young monkeys. Upon further analysis of adult liver tissue after 36 mo, hepatic mRNA expression of proteins related to inflammation and hepatic response to injury (nuclear factor kappa-light-chain-enhancer of activated B cells (*NFκB*), hepatocyte growth factor (*HGF)*, and transforming growth factor-β (*TGFβ))*) were significantly greater in treated animals compared to controls, with no further evidence of clinical, hematological, or histological evidence of liver damage.

According to a QSAR model described in an ECHA dossier, the oral lowest-observed-adverse-effect-level (LOAEL) for Copper Gluconate in rats was predicted to be 94.7 mg/kg bw/d.[3] Based on this value and the Classification, Labelling, and

Packaging (CLP) regulation, the specific target organ toxicity for repeated exposure-2 (STOT RE-2) designation, indicating presumed toxicity to specific organs with repeated exposure, was considered applicable.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Details on the oral developmental and reproductive toxicity studies and computational studies to predict such toxicity for Copper Gluconate summarized below are found in Table 5.

Groups of male albino rats (8/group) were used to examine the toxicological effects of Copper Gluconate upon oxidative biomarkers in testis tissue in a 90-d reproductive toxicity study.[30] The animals received 3.75, 7.5, or 15 mg/kg/d Copper Gluconate, via gavage; 2 control groups received either 1 ml of saline or 0.5 ml dimethyl sulfoxide (DMSO), via gavage, for the duration of the study. Treatment with Copper Gluconate did not significantly affect catalase levels but did significantly reduce glutathione and superoxide dismutase levels (at the medium and high dose). Additionally, malondialdehyde levels were also increased in treated rats, compared to controls; the study results are indicative of the development of oxidative stress in testes tissue. Female Swiss-Webster mice (20/group) and female albino Wistar rats (number/group not specified) received 0, 0.1, 3, or 30 mg/kg/d Copper Gluconate, via gavage, from day 6 to 14 of gestation or from day 5 to 15 of gestation, respectively, in two separate developmental oral toxicity studies.[27,28] Neither embryotoxic nor teratogenic effects were observed in treated animals compared to controls in either study. In another oral developmental toxicity study, female Wistar rats (20/group) received up to 30 mg/kg/d Copper Gluconate, via gavage.[27,28] Female rats were dosed with Copper Gluconate 15 d prior to mating, during gestation, and for 21 d postpartum. Groups of treated females, from each dose group, were mated with untreated males. To assess the effects of Copper Gluconate on the male rat, 2 additional groups of males that were treated with 3 mg/kg/d Copper Gluconate 60 d prior to mating were mated with a group of untreated females or with a group of females that received the same 60-d pre-treatment. A third group of untreated males mated with untreated females served as controls. Male rat reproductive performance was not affected by Copper Gluconate administration. No significant differences were observed between the percentage of pregnancies, the number and distribution of embryos in each uterine horn, implantation sites, resorption sites, duration of gestation, mean number of fetuses and live pups per litter, litter size, stillborn and live born numbers, gross anomalies and mean weight per pup, compared to controls. Necropsy of dams and pups revealed a lack of visceral abnormalities. Thus, under the conditions of the study, the researchers concluded that Copper Gluconate did not affect the reproductive performance of either male or female rats.

As described in an ECHA dossier, 2 separate models following the REACH Guidance on QSARs and Grouping of Chemicals R.6 were used to predict the developmental and reproductive toxicity of Copper Gluconate in rats.[3] The no-observed-adverse-effect-level (NOAEL) of Copper Gluconate for oral reproductive toxicity in rats was predicted to be 318 mg/kg bw/d and the NOAEL of Copper Gluconate for oral developmental toxicity in rats was predicted to be 793 mg/kg bw/d.

GENOTOXICITY STUDIES

In Vitro

Copper Gluconate was tested at up to 1 mg/plate using *Salmonella typhimurium* strains TA97 and TA102 in an Ames test.[3] The test article was not genotoxic, with or without metabolic activation. Additionally, Copper Gluconate was evaluated for mutagenicity in various in vitro tests using *S. typhimurium* strains TA1535, TA1537, and TA1538, and *Saccharomyces cerevisiae* strain D4.[27,28] The test article was not considered mutagenic, with or without metabolic activation. No further details were provided.

Computational

QSAR model results predicting the genotoxic potential of Copper Gluconate were described in an ECHA dossier.[3] Using QSAR Toolbox 3.4.0.17, and based on REACH guidance R.6, Copper Gluconate was predicted to be non-genotoxic in an Ames test (with and without metabolic activation) and in a chromosome aberration test. Based on the expert rule-based system, Derek Nexus 6.3.0, Copper Gluconate exposure is not predicted to cause in vivo mutagenicity (*Mutagenicity in vivo* endpoint).[CIR staff]

CARCINOGENICITY STUDIES

Tumor Promotion

Five-wk-old male Fischer 344 rats (9 - 12/group) were given a single intraperitoneal injection of 200 mg/kg bw *N*-nitroso-diethylamine (DEN) as a carcinogenic initiator, and after 2 wk, received 0, 0.001, 0.03, or 0.6% (0, 10, 300, or 6000 mg/kg/d) Copper Gluconate in a basal diet for 6 wk, in a medium-term liver carcinogenicity bioassay.[25] Simultaneously, two additional groups which did not receive the nitrosamine injection prior were fed 0 or 0.6% Copper Gluconate in the diet. Numbers of glutathione *S*-transferase placental form (GST-P) positive lesions, single GST-P-positive hepatocytes, 8-oxoguanine-positive hepatocytes, and levels of cell proliferation and apoptosis in the liver were significantly increased in the 0.6% Copper Gluconate group, with and without nitrosamine pre-treatment. Furthermore, the hepatic mRNA expression of the metal metabolism-related gene *Mt1a*, the apoptosis-related genes *Gadd45α* and *p21*, the inflammation-related genes *TNF*-α, *IL-1*α,and *Nos2*, and *c-fos* were significantly increased in the 0.6% group, irrespective of nitrosamine treatment, while *p53* expression was significantly increased in the 0.03 and 0.6% Copper Gluconate groups which received the nitrosamine injection and in the 0.6% group which did not

receive the nitrosamine injection. In the absence of the DEN treatment, animals treated with Copper Gluconate did not develop GST-P-positive lesions in the liver. While treatment with Copper Gluconate may have been associated with carcinogenic risk toward the liver at a high dose level (0.6%), the researchers indicated there is a considerably large safety margin for Copper Gluconate at the human relevant dose of 0.001 and 0.03% (the 0.001% dose nearly corresponds to the daily human intake of Copper Gluconate, as a food additive).

Groups of male Brl:Han Wistar rats (3 rats/group) were used to evaluate the toxicologic and carcinogenic risk of Copper Gluconate in a 13-wk medium-term multi-organ carcinogenesis assay.[31] Throughout the experiment, animals were fed a diet containing 0, 0.1, 0.3, 0.48, or 0.6% (equivalent to 0, 1000, 3000, 4800, or 6000 mg/kg/d, respectively) Copper Gluconate, or 1.2% (12,000 mg/kg/d; 1 animal) Copper Gluconate, while being exposed to multiple carcinogens. All animals received a single intraperitoneal administration of 100 mg/kg bw DEN followed by 4 intraperitoneal injections of 20 mg/kg bw *N*-methylnitrosourea (MNU) and 0.05% *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BBN), administered in drinking water, during the initial 2 wk. In the following 2 wk, the animals received 4 subcutaneous injections of 40 mg/kg bw 1,2-dimethylhydrazine (DMH) and 0.1% 2,2'-dihydroxy-di-*n*-propylnitrosamine (DHPN), in drinking water. The animals were killed and necropsied after 13 wk. Blood samples were taken from the abdominal aorta, urine samples were taken from the bladder, and major organs and tissues were removed; the liver was weighed and fixed for histopathological, histochemical, and immunohistochemical analyses. All animals survived until killed. Body weight and food consumption were similar between groups. Black stool was found in rats exposed to ≥ 0.3% Copper Gluconate. Copper levels in the serum, urine, and liver were significantly increased in animals dosed with ≥ 0.6% Copper Gluconate. Absolute and relative liver weights were similar among groups but appeared to increase in the 1 animal that received 1.2% Copper Gluconate. Livers were macroscopically and histologically normal in the groups dosed with ≤ 0.48%; slight or moderate granulomas were scattered in livers of animals in the 0.6% group. Copper accumulation and metallothionein induction were apparent at doses of ≥ 0.3% and ≥ 0.1% Copper Gluconate, respectively. Marked diffuse granulomas and hepatocellular necrosis were observed in the liver of the animal in the 1.2% Copper Gluconate group (1 rat in this group). Putative preneoplastic lesions appeared in the rat dosed with 1.2% Copper Gluconate and 8-hydroxydeoxyguanosine formation was enhanced in the 0.6% group. The researchers indicated that under the current experimental conditions with co-exposure to multiple carcinogens, Copper Gluconate did not exert significant systemic toxicity, i.e., there were no differences in mean body weights among groups and in any treatment-related alternations in extrahepatic organs/tissues; however, it was noted that Copper Gluconate may cause toxic and carcinogenic risks towards the liver at high doses.

OTHER RELEVANT STUDIES

Nephrotoxicity

In a 90-d oral toxicity study examining the effects of Copper Gluconate on renal function, groups of 8 male albino Swiss rats were administered 3.75, 7.5, or 15 mg/kg Copper Gluconate, in saline, via gavage.[32] Controls received either 1 ml saline or 0.5 ml DMSO. Two animals per group were killed and blood samples were collected via cardiac puncture on days 30, 45, 60, and 90 for serum analysis. A statistically significant increase in urea, creatinine, sodium, and potassium levels was observed in renal serum obtained from treated animals, compared to controls. The results indicated development of renal failure and oral ingestion of the test article was considered nephrotoxic.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details of the human repeated-insult patch tests (HRIPT) and computational studies on Copper Gluconate summarized below are found in Table 6.

A leave-on baby product formulation and a rinse-off adult product formulation, each containing 0.00008% Copper Gluconate (dose/unit area: 0.00004 mg/cm^2), were found to be non-irritating and non-sensitizing when applied neat in 2 separate HRIPTs, using 210 and 211 subjects, respectively.[33,34] A powder containing 0.1% Copper Gluconate (up to 0.038 mg/cm^2) was not irritating or sensitizing when applied in distilled water to 52 subjects in an HRIPT.[35] A rinse-off baby product formulation containing 0.2% Copper Gluconate (0.1 mg/cm^2) was also non-irritating and non-sensitizing when applied neat in an HRIPT using 217 subjects.[36] Based on QSAR models described in an ECHA dossier, Copper Gluconate was predicted to produce a primary dermal irritation index (PDII) of 2.26 in rabbit skin and 5.08% Copper Gluconate was predicted to be the effective concentration needed to induce a 3-fold increase in local lymph node proliferative activity (EC3) in a mouse skin model.[3] Based on an EC3 value > 2%, Copper Gluconate was classified according to Globally Harmonized System (GHS) criteria as having low to moderate skin-sensitizing potential (Skin Sensitizer Category 1B, under GHS category 1: substances that show a low to moderate frequency of occurrence in humans and/or low to moderate potency in animals and can be presumed to potentially produce significant sensitization in humans.[3,37]

OCULAR IRRITATION STUDIES

Details of the in vitro and computational ocular irritation studies described below can be found in Table 7.

The potential for a face cream containing 0.0025% Copper Gluconate to cause ocular irritation was evaluated in a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay using an in vitro tissue model.[38] EpiOcular™ tissues were

treated with the test article for up to 24 h. More than 24 h of treatment time was required to achieve a 50% reduction in tissue cell viability; the test article was classified as minimally or not irritating to eyes. Using QSAR prediction software (QSAR Toolbox 3.4.0.17) and the REACH guideline on QSAR, the modified maximum average score (MMAS) for Copper Gluconate was predicted to be 49.5 in rabbit eyes.[3] Copper Gluconate was predicted to be mildly toxic, considering that the maximum value for damage to the cornea, conjunctiva, and iris is 110. Based on GHS criteria, Copper Gluconate was considered to be a potential mild irritant to the eyes (Category 2B).

CLINICAL STUDIES

Oral Supplementation

The effect of copper supplementation, in the form of Copper Gluconate, was evaluated in a 12-wk, double-blind, randomized study.[39] Seven subjects (3 men and 4 women) received either a 5 mg capsule of Copper Gluconate or placebo twice a day. Blood, serum, urine, and hair samples were collected at the beginning of the study, 6 wk after supplementation, and at the end of the 12 wk. Copper, zinc, and magnesium levels were determined in all the samples; no significant changes were observed in serum, urine, or hair for the study duration. No significant changes in hematocrit, mean corpuscular volume, serum cholesterol, triglyceride, glutamic-oxaloacetic transaminase, alkaline phosphatase, gamma-glutamyl transferase, or lactate dehydrogenase levels were observed in treated subjects. Serum potassium levels did change from a mean of 4.3 mEq/l to 4 mEq/l ($p < 0.05$). The incidence of nausea, diarrhea, and heartburn was the same in both treated subjects and controls.

EXPOSURE ASSESSMENT

Copper is an essential mineral, which is naturally present in some foods and can also be taken as a dietary supplement. As a food additive, Copper Gluconate may serve as a nutritional supplement for copper.[17] The daily copper intake needed to fulfill the nutritional needs averages 900 µg/d for adults (aged 19+ yr) and 340 µg/d for babies (aged 1-3 yr). Additionally, the highest daily intake that is unlikely to lead to adverse health effects is set at 10,000 µg/d for adults (aged 19+ yr) and 1000 µg/d for babies (aged 1-3 yr).

CIR staff applied exposure parameters identified from literature and the in silico tool VERMEER Cosmolife (previously named SpheraCosmolife)[40] to estimate the daily exposure to copper that results from the highest concentration of Copper Gluconate used in two product categories: skin cleansing preparations and non-spray night products. The following exposure parameters are retrieved from the SCCS NoG [41] and relevant published literature.[42,43]

i) Copper Gluconate at 0.1% in skin cleansing preparations (e.g., make-up remover)

Estimated daily amount of make-up remover applied: 5 g/d = 5000 mg/d
Retention factor: 0.1
Type of exposure: rinse-off
Surface area for application: 565 cm^2 (½ area head - female)
Relative daily exposure of make-up remover: 5000 mg/d × 0.1 (retention factor) = 500 mg/d
Exposure to Copper Gluconate as used in make-up remover: 500 mg/d × 0.1% (use concentration) = 0.5 mg/d
Daily exposure to copper from Copper Gluconate in make-up remover: 0.5 mg/d × 14% = 0.07 mg/d = 70 µg/d
SED with a conservative dermal absorption rate of 100%: 70 µg/d
Skin surface exposure: 70 µg/d ÷ 565 cm^2 = 0.124 µg/cm^2/d

ii) Copper Gluconate at 0.008% in non-spray night products (e.g., body lotion, leave-on)

Estimated daily amount of body lotion applied: 7.82 g/d = 7820 mg/d
Retention factor: 1.0
Type of exposure: leave-on
Surface area for application: 15,670 cm^2 (area body and area head - female)*

Relative daily exposure of body lotion: 7820 mg/d × 1.0 (retention factor) = 7820 mg/d
Exposure to Copper Gluconate as used in body lotion: 7820 mg/d × 0.008% (use concentration) = 0.6256 mg/d
Daily exposure to copper from Copper Gluconate in body lotion: 0.6256 mg/d × 14% = 0.0876 mg/d = 87.6 µg/d
SED with a conservative dermal absorption rate of 100%: 87.6 µg/d
Skin surface exposure: 87.6 µg/d ÷ 15,670 cm^2 = 0.0056 µg/cm^2/d

* As surface area of the body to which the night product is applied is unknown, whole-body exposure is being assumed as a conservative approach.

The exposure assessment indicates that the daily exposure to copper from Copper Gluconate in make-up removers, and body lotions does not exceed 70 µg/d and 87.6 µg/d, respectively. These exposure levels are substantially below the RDA of 900 µg/d for adults or 340 µg/d for babies (1-3 yr), as well as the TUL of 10,000 µg/d for adults or 1000 µg/d for babies.

SUMMARY

The safety of Copper Gluconate is reviewed in this safety assessment. As per the *Dictionary*, this ingredient is reported to function as a skin conditioning agent in cosmetics. According to RLD that CIR received in 2024, Copper Gluconate is used in 666 formulations, with the majority of the uses (492) in skin care preparations. VCRP survey data received in 2023 reported Copper Gluconate to be used in 170 formulations, 140 of which are in leave-on formulations. The results of the concentration of use survey conducted by the Council in 2022 and updated in 2024 indicate that the maximum reported concentration of use for Copper Gluconate in a leave-on formulation is 0.008% in non-spray night products; overall, the highest maximum reported concentration of use is 0.36% in other oral hygiene products. Copper is an essential mineral which is naturally found in the human body and in foods; the RDA and TUL for adult copper intake is 900 µg and 10,000 µg/d, respectively. Notably, Copper Gluconate is considered GRAS as a direct food substance for human consumption, which includes use in nutrient supplements and in infant formula.

Groups of male C57BL/6J mice (5/group) were administered 0.005 M Copper Gluconate in drinking water for 92 d. A statistically significant increase in copper accumulation in the livers of Copper Gluconate-fed mice was observed, compared to controls. Differences between the amount of copper found in the kidney, brain, and heart of Copper Gluconate-fed mice, compared to controls (drinking water) were not statistically significant. Groups of male C57BL/6J mice (5 -7/group) were administered 0.005 M Copper Gluconate in drinking water for 104 d, starting from 64, 302, and 540 days of age. The difference between copper accumulation in the liver of Copper Gluconate-fed mice and control mice was statistically significant in all 3 age groups; no statistically significant differences were observed in copper accumulation in the kidneys (in all 3 age groups), compared to controls. In a biodistribution study of copper, male Wistar rats received a single dose of 79.5 mg/kg Copper Gluconate, dissolved in deionized water, via gavage and were observed for up to 168 h. A C_{max} of 2.93 ± 0.21 µg copper/g in brain striatum tissue at 0.25 h returned to baseline after 168 h. No significant differences in copper concentration in the midbrain tissue of treated and control rats was observed. The C_{max} of copper in the Copper Gluconate-treated liver was 391% higher than baseline (elimination and redistribution of copper occurred 24 h after administration) and the AUC value for copper in the liver was about 200 times greater than the AUC for plasma copper concentration (494.8 ± 47.22 vs. 2.48 ± 0.36 µg/ml*h).

Wilson's disease and Menkes disease are rare genetic defects characterized by abnormal copper metabolism in the human body. Wilson's disease is a defect in copper excretion leading to progressive accumulation of toxic levels in the liver, brain, kidneys, and cornea. Menkes disease is a severe and fatal sex-linked mutation in genes coding for the copper-transport protein that results in copper deficiency in male infants.

No significant differences in weight gain or hepatic enzyme activity were observed in male Wistar rats that were administered a single oral dose of 79.5, 156, or 312 mg/kg Copper Gluconate. The survival rate of rats in the 312 mg/kg group was 31%; no animals in the 79.5 or 156 mg/kg groups died. Male and female Wistar rats received a single dose of 1800, 2400, or 3200 mg/kg bw Copper Gluconate, in water, via gavage, in another acute oral toxicity study. Five out of 10 of the animals from the 1800 mg/group died within 48 h of exposure, 8 out of 10 animals in the 2400 mg/group died within 48 h of exposure, and all 10 animals from the 3200 were found dead within 24 h of dosing. The acute oral LD_{50} was determined to be 1709 mg/kg bw (males and females combined). An acute dermal LD_{50} of 2130 mg/kg Copper Gluconate was predicted for rats, based on a QSAR model.

No differences in final body weight, liver weight, food consumption, or gross or histological changes were observed in male Fischer 344 rats (5/group) that were administered 0, 0.001, 0.03, or 0.6% Copper Gluconate in the diet for 2 wk in a short-term oral toxicity study. Hepatic mRNA expression of *Mt1a* and *Gadd45α* were significantly increased in the 0.6% group and *p21* expression was significantly increased in the 0.3 and 0.6% groups; other gene expression levels were unaffected.

Male and female rats that were administered 0.006 or 0.06% Copper Gluconate in the diet for 24 wk exhibited no adverse effects in food consumption, body weight gain, urine analysis, or gross or microscopic examination of tissues and organs; copper content was elevated in the kidneys of animals in the 0.06% Copper Gluconate group. Groups of 25 male and female rats received 1.14% Copper Gluconate in the diet for up to 44 wk in a chronic oral toxicity study. Significant growth retardation was discernable at 26 wk, compared to controls, and over 80% of the animals died by week 35. Hypertrophied uteri, ovaries, seminal vesicles and hypertrophied stomachs, occasional ulcers, bloody mucus in the intestinal tract, and bronzed kidneys and livers were observed upon necropsy; chronic exposure to 1.14% Copper Gluconate in the diet was considered toxic. Male and female Beagle dogs (6/sex/group) were administered 0.012, 0.06, or 0.24% Copper Gluconate, in the diet, for up to 1 yr; aside from copper accumulation in the liver, kidney, and spleen of animals in the 0.24% group, and reversible minimal liver function in 1 dog from the 0.24% group, no other test-article related effects were observed. The survival curve and lifespan of male C57BL/6J mice (number not specified) which received 0.0005, 0.001, or 0.005 M Copper Gluconate in drinking water during the lifetime were significantly reduced by up to 11.8, 14.7 and 14.4%, respectively, indicating the absence of a dose-response relationship for survival. No differences in food intake, body weight, or weight gain by age or time of exposure were observed in adult Capuchin

monkeys (2/sex) that were fed up to 7.5 mg/d copper, and in young Capuchin monkeys (2/sex) fed up to 5.5 mg/d copper (as Copper Gluconate), in a 3-yr oral toxicity study. In the adult monkeys, the hepatic mRNA expression of proteins related to inflammation and hepatic response to injury (*NFκB*, *HGF*, and *TGFβ*) were significantly greater in treated animals compared to controls, with no further evidence of clinical, hematological, or histological evidence of liver damage. Using a QSAR model, the oral LOAEL for Copper Gluconate in rats was predicted to be 94.7 mg/kg bw/d; toxicity to specific organs with repeated exposure, as outlined in the specific target organ toxicity for repeated exposure-2 designation, was considered applicable.

Male albino rats (8/group) received 3.75, 7.5, or 15 mg/kg/d Copper Gluconate, via gavage, in a 90-d reproductive toxicity study. Oxidative biomarkers in rat testis tissue revealed that Copper Gluconate did not significantly affect catalase levels but did significantly reduce glutathione and superoxide dismutase levels (at the medium and high dose), while increasing malondialdehyde levels, compared to controls. These findings indicated the development of oxidative stress. In two separate developmental oral toxicity studies, neither embryotoxic nor teratogenic effects were observed in female Swiss-Webster mice (20/group) or female albino rats (number not specified) that received 0, 0.1, 3, or 30 mg/kg/d Copper Gluconate, via gavage, during gestation. Groups of female Wistar rats (20/group), mated with untreated males and males treated with 3 mg/kg/d Copper Gluconate (both 10/group), received up to 30 mg/kg/d Copper Gluconate in another developmental toxicity study. No significant differences were observed between the percentage of pregnancies, the number and distribution of embryos in each uterine horn, implantation sites, resorption sites, duration of gestation, mean number of fetuses and live pups per litter, litter size, stillborn and live born numbers, gross anomalies and mean weight per pup, compared to controls. Under the conditions of this study, Copper Gluconate did not affect the reproductive performance of either male or female rats. Based on 2 QSAR models described in an ECHA dossier, the NOAEL of Copper Gluconate for oral reproductive toxicity in rats was predicted to be 318 mg/kg bw/d and the NOAEL of Copper Gluconate for oral developmental toxicity in rats was predicted to be 793 mg/kg bw/d.

Copper Gluconate was not genotoxic when tested at up to 1 mg/plate in *S. typhimurium* TA97 and TA102 strains, with or without metabolic activation, in an Ames test. Additionally, Copper Gluconate was not mutagenic when evaluated in various in vitro tests using *S. typhimurium* strains TA1535, TA1537, TA1538, and *S. cerevisiae* strain D4, with or without metabolic activation. In a QSAR Toolbox 3.4.0.17 prediction described in an ECHA dossier, Copper Gluconate was predicted to be non-genotoxic in an Ames test (with and without metabolic activation) and in a chromosome aberration test. Additionally, based on the expert rule-based system, Derek Nexus 6.3.0, Copper Gluconate is not predicted to be mutagenic.

After an injection with DEN, male Fischer 344 rats (9 – 12 /group) received 0, 0.001, 0.03, or 0.6% Copper Gluconate in a basal diet for 6 wk in a medium-term liver carcinogenicity bioassay. Numbers of GST-P-positive lesions, single GST-P-positive hepatocytes, 8-oxoguanine-positive hepatocytes, and levels of cell proliferation and apoptosis in the liver were significantly increased in the 0.6% Copper Gluconate group, with and without nitrosamine pre-treatment. The hepatic mRNA expression of *Mt1a, Gadd45α*, *p21*, *TNF- α, IL -1α, Nos2*, and *c-fos* were significantly increased in the 0.6% group, irrespective of nitrosamine treatment, while *p53* expression was significantly increased in the 0.03% and 0.6% groups which received the nitrosamine injection and in the 0.6% group which did not receive the nitrosamine injection. While treatment with Copper Gluconate may have been associated with carcinogenic risk toward the liver at the 0.6% dose, the researchers noted a considerably large safety margin for Copper Gluconate at the human relevant dose of 0.001 and 0.03% (0.001% nearly corresponding to the daily human intake, as a food additive).

In a 13-wk medium-term, multi-organ carcinogenesis assay, male Brl:Han Wistar rats (3/group) were fed a diet containing 0, 0.1, 0.3, 0.48, 0.6, or 1.2% Copper Gluconate, while being exposed to multiple carcinogens (DEN, MNU, DMH, and DHPN). Black stool was found in rats exposed to ≥ 0.3% Copper Gluconate, copper levels in the serum, urine, and liver were significantly increased in rats dosed with 0.6% Copper Gluconate, and marked diffuse granulomas and hepatocellular necrosis were observed in the liver of the single (1) rat in the 1.2% Copper Gluconate group. Copper Gluconate did not exert significant systemic toxicity; however, it was noted that Copper Gluconate may cause toxic and carcinogenic risks to the liver at high doses.

In a 90-d oral toxicity study, evaluating the effects of Copper Gluconate on renal function, a statistically significant increase in renal urea, creatine, sodium, and potassium levels was observed in male albino Swiss rats (8/group) that were administered 3.75, 7.5, or 15 mg/kg Copper Gluconate, in saline, via gavage. These results were indicative of renal failure and the test article was considered nephrotoxic.

A leave-on baby product formulation and a rinse-off adult formulation, each containing 0.00008% Copper Gluconate (0.00004 mg/cm^2) and a rinse-off baby product formulation containing 0.2% Copper Gluconate (0.1 mg/cm^2) were not irritating or sensitizing when tested neat in 3 separate HRIPTs using 210, 211, and 217 subjects, respectively. A powder formulation containing 0.1% Copper Gluconate (up to 0.038 mg/cm^2) was not irritating or sensitizing when tested in distilled water in an HRIPT using 52 subjects. Based on a QSAR model described in an ECHA dossier, the PDII of Copper Gluconate was predicted to be 2.26 in rabbit skin. In another QSAR-based prediction described in an ECHA dossier, Copper Gluconate was predicted to produce an EC3 value of 5.08% in an in vivo LLNA of mice; the test article was predicted to have low to moderate skin-sensitizing potential.

The ocular irritation potential of a face cream containing 0.0025% Copper Gluconate was evaluated in an MTT assay using an in vitro tissue model. The test article was classified as minimally or not irritating to the eyes. Based on a QSAR model for

ocular irritation, the MMAS for Copper Gluconate in rabbit eyes was predicted, as described in an ECHA dossier, to be 49.5 out of a maximum damage value of 110; the test article was considered to be a potential mild irritant to the eyes.

In a 12-wk, double-blind, randomized clinical trial, subjects received either a 5 mg capsule of Copper Gluconate or placebo, twice a day. No significant changes in copper, zinc, and magnesium levels were observed in the serum, urine, or hair. Similarly, no significant changes in hematocrit, mean corpuscular volume, serum cholesterol, triglyceride, glutamic-oxaloacetic transaminase, alkaline phosphatase, gamma-glutamyl transferase, or lactate dehydrogenase levels were observed in treated subjects. Serum potassium levels did change from a mean of 4.3 mEq/l to 4 mEq/l ($p < 0.05$). The incidence of nausea, diarrhea, and heartburn was the same in both treated subjects and controls.

Using the in silico tool, VEERMEER Cosmolife, daily exposures to copper from Copper Gluconate were estimated to not exceed 151.2 µg/d in mouthwash, 70 µg/d in make-up removers, and 87.6 µg/d in body lotions. These exposure levels are substantially lower than the RDA values for copper in adults and babies (900 and 340 µg/d), as well as corresponding TUL values (10,000 µg/d and 1000 µg/d).

DISCUSSION

This assessment reviews the safety of Copper Gluconate as used in cosmetic formulations, in accordance with the product categories and concentrations of use identified in the Use section and Use table. The Panel noted that there is a paucity of genotoxicity data in this safety assessment, and only oral tumor promotion studies using high doses of Copper Gluconate are available. While some carcinogenic effects were observed in these studies, along with nephrotoxic effects in a gavage study, the concentrations at which these adverse effects were observed are much greater than those used in cosmetic formulations. The US FDA has designated Copper Gluconate as GRAS as a direct food ingredient, and the Panel noted copper is an essential nutrient. Additionally, Copper Gluconate is not a dermal irritant or dermal sensitizer in several HRIPTs. The Panel considered these findings, coupled with the low concentration of use in cosmetic products and negative developmental and reproductive toxicity data, and determined that the data were sufficient to conclude that Copper Gluconate is safe in cosmetics in the present practices of use and concentration.

The Panel expressed concern regarding other heavy metals that may be present in this ingredient. They stressed that the cosmetics industry should continue to use the necessary procedures to minimize impurities in cosmetic formulations according to limits set by the US FDA and EPA.

The Panel also discussed the issue of incidental inhalation resulting from exposure to this ingredient; for example, Copper Gluconate is reported to be used in face powder formulations (concentration not provided) and could possibly be inhaled. Inhalation toxicity data were not available. However, coupled with the small actual exposure in the breathing zone and the low concentrations at which this ingredient is used (or is expected to be used) in potentially inhaled products, the available information indicates that the 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.

As stated in the Use section, products containing this ingredient may be marketed for use with airbrush delivery systems. While it may be known in some (but not all) instances whether or not there is use in airbrush applications, information regarding the consumer habits and practices data, product particle size data, and/or other relevant particle data (e.g., diameter) related to this use technology are absent, and thus the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Copper Gluconate is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

TABLES

Table 1. Chemical properties

Property	Value	Reference
Physical Form	solid; crystalline powder powder fine powder	3,4 5 21CFR184.1260
Color	light blue to bluish-green green	3,4 21CFR184. 1260 5
Odor	odorless	3,4
Formula Weight (g/mol)	453.9 (compared to 63.55 g/mol atomic weight of copper)	6,7
Topological Polar Surface Area (Å2)	283	4
Density (g/ml @ 20 ºC)	1.78	3
Vapor pressure (mmHg @ 20 ºC)	0.01	3
Melting Point (ºC)	155 - 157	3,4
Water Solubility (g/l @ 25 °C)	300	3,4
Solubility *Soluble* *Insoluble*	 water, alcohol (slightly) acetone, ether, organic solvents	3,4
log K_{ow}	-2.98 (estimated)	3

Table 2. Frequency (RLD/VCRP) and concentration of use of Copper Gluconate according to likely duration and exposure and by product category

	# of Uses		Max Conc of Use
	RLD (2024)[13]	VCRP (2023)[14]	% (2022)[15]
Totals*	**666**	**170**	**0.000025 - 0.36**
summarized by likely duration and exposure**			
Duration of Use			
Leave-On	***	*140*	*0.00008 - 0.008*
Rinse-Off	***	*30*	*0.000025 - 0.36*
Diluted for (Bath) Use	***	*NR*	*NR*
Exposure Type			
Eye Area	***	13	0.0005 - 0.006
Incidental Ingestion	***	6	0.36
Incidental Inhalation-Spray	***	53[a]; 46[b]	0.0008[b]
Incidental Inhalation-Powder	***	5; 46[b]	0.0008[b]; 0.0008 - 0.003[c]
Dermal Contact	***	156	0.0008 - 0.1
Deodorant (underarm)	***	NR	NR
Hair - Non-Coloring	***	8	0.000025 - 0.0008
Hair-Coloring	***	NR	NR
Nail	***	NR	NR
Mucous Membrane	***	8	0.36
Baby Products	***	2	0.00008
as reported by product category			
Baby Products	***1***		
Baby Shampoos	NR	2	0.00008
Baby Lotions/Oils/Powders/Creams	1	NR	0.00008
Eye Makeup Preparations (other than children's eye makeup preparations)	***26***		
Eyeliner	15	NR	0.006
Eye Lotion	8	7	0.0005
Eye Makeup Remover	1	1	0.0008
Mascara	1	NR	NR
Other Eye Makeup Preparations	1	5	NR
Fragrance Preparations	***1***		
Cologne and Toilet Water	1	NR	NR
Hair Preparations (non-coloring)	***44***		
Hair Conditioners	8 (l.o.) 6 (r.o.)	NR	0.000025
Rinses (non-coloring)	1	NR	0.0008
Shampoos (non-coloring)	13 (r.o.)	4	0.000025
Tonics, Dressings, and Other Hair Grooming Aids	8	1	NR
Other Hair Preparations	10 (l.o.) 2 (r.o.)	1	NR
Hair Coloring Preparations	***1***		
Other Hair Coloring Preparation	1 (r.o.)	NR	NR
Makeup Preparations (not eye; not children's)	***62***		
Blushers and Rouges (all types)	3	2	NR
Face Powders	1	5	NR
Foundations	31	5	NR
Lipsticks and Lip Glosses	3	2	NR
Makeup Bases	NR	1	NR
Makeup Fixatives	4	3	NR
Other Makeup Preparations	20 (l.o.)	4	0.0025
Oral Products	***3***		
Mouthwashes and Breath Fresheners (liquids and sprays)	NR	4	NR
Other Oral Products	3	NR	0.36
Personal Cleanliness	***10***		
Bath Soaps and Body Washes	8	1	NR
Disposable Wipes	NR	NA	NR
Other Personal Cleanliness Products	2 (l.o.)	1	NR
Shaving Preparations	***4***		
Aftershave Lotions	3	NR	NR
Other Shaving Preparation Products	1	NR	NR
Skin Care Preparations (creams, lotions, powder, and sprays)	***492***		
Cleansing (cold creams, cleansing lotions, liquids, and pads)	38	17	0.0016 - 0.1
Face and Neck (excluding shaving preparations)	322 (l.o.) 54 (r.o.)	39	0.0008 - 0.003
Body and Hand (excluding shaving preparations)	38 (l.o.) 4 (r.o.)	7	0.0008
Moisturizing	68	35	0.0025
Night	9	5	0.005-0.008
Paste Masks (mud packs)	10	NR	0.0001-0.005
Skin Fresheners	9	7	NR

Table 2. Frequency (RLD/VCRP) and concentration of use of Copper Gluconate according to likely duration and exposure and by product category

	# of Uses		Max Conc of Use
	RLD (2024)[13]	**VCRP (2023)**[14]	**% (2022)**[15]
Other Skin Care Preparations	23 (l.o.) 7 (r.o.)	10	0.0005
Suntan Preparations	***27***		
Suntan Gels, Creams, and Liquids	25	NR	NR
Indoor Tanning Preparations	2	NR	NR
Other Preparations (i.e., those preparations that do not fit another category)	***3***	NA	

NR – not reported; NA – not applicable (this category was not part of the VCRP)
l.o. – leave-on; r.o. – rinse-off
*The total FOU provided for RLD refers to the ingredient count supplied by FDA, and is not a summation of the number of uses per category because each product may be categorized under multiple ***product*** categories. For data supplied via the VCRP or by the Council survey, the sum of all exposure types may not equal the sum of total uses because each ingredient may be used in cosmetics with multiple ***exposure*** types.
**Likely duration and exposure are derived from VCRP and survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
***In the RLD each ingredient may be reported under several product categories, making a summation of RLD misleading in comparison to VCRP data. Accordingly, RLD are presented below by product category (as supplied by FDA), but are not summarized by likely duration and exposure.
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.
[c] 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

Table 3. Acute toxicity studies on Copper Gluconate

Vehicle	Animals/Group	Dose	Protocol	LD_{50}/Results	Reference
			ORAL		
deionized water	Male Wistar rats (4 - 6/group)	79.5, 156, or 312 mg/kg	Administered via gavage; body weights were recorded for 7 d. Animals were killed on day 7 and samples from the blood and liver were obtained for analysis. Controls received equivalent doses of calcium gluconate.	No animals from the 79.5 and 156 mg/kg groups died. No significant differences in weight gain or hepatic activity (measured via GGT and ALT levels) were observed compared to the control group. Survival rate for the 312 mg/kg group was 31%.	23
water	Wistar rats (5/sex/group)	0, 1800, 2400, or 3200 mg/kg bw	OECD TG 401; administered via gavage; animals were observed for up to 14 d.	LD_{50} = 1709 mg/kg bw (combined for males and females) 5 animals in the 1800 mg/kg group died within 48 h; all animals in the 2400 and 3200 mg/kg died within 48 or 24 h, respectively In the animals that were found dead, local hemorrhages and necrosis were found in the fundus of the stomach, and the intestinal tracts were congested; surviving animals did not exhibit any treatment-related gross abnormalities upon necropsy.	3
			COMPUTATIONAL		
NA	NA	NA	Results from a QSAR model (described in an ECHA dossier); based upon REACH Guidance QSAR R6; was used to predict the acute dermal LD_{50} in rats.	LD_{50} = 2130 mg/kg bw (dermal)	3

Table 4. Repeated dose toxicity studies on Copper Gluconate

Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
				ORAL		
feed	Male Fischer 344 rats (5/group)	2 wk	0, 0.001, 0.03, or 0.6% (0, 10, 300, or 6000 ppm)	The liver was removed and weighed upon study termination. Liver tissue was fixed for histopathological analysis and the remainder was assessed for genes related to metal metabolism (*Mt1a*), apoptosis (*Gadd45α*, *p21*, *p53*), inflammation (*TNF*-α, *IL-1*α, *Nos2*), and normal cell growth (*c-fos*).	The test article did not affect final body weight, liver weight, or food consumption and no gross or histological changes were observed in the liver of treated animals, compared to controls. Hepatic mRNA expression of metal metabolism-related gene *Mt1a* and apoptosis-related gene *Gadd45α* were significantly increased in the 0.6% group. The expression of apoptosis-related gene *p21* was significantly increased in the 0.03 and 0.6% groups. The expression of *p53* (apoptosis-related), *TNF*- α, *IL-1*α, *Nos2* (inflammation-related), and *c-fos* (related to cell growth) expression were not affected at any dose level.	25
feed	Male and female rats (number not specified)	6 mo (24 wk)	0.006 or 0.06% in the diet (mean consumption of 3.46 or 34.9 mg/kg/d)	No further details were provided.	No adverse effects were noted in food consumption, body weight gain, urinalysis, or gross and microscopic examination of tissues and organs at necropsy. Copper content was elevated in the kidneys of test animals fed the test diet.	26
feed	Rats (25/sex/group)	Up to 44 wk	1.14% in the diet (equivalent to 0.16% copper)	A control group was also maintained. No further details were provided.	Significant growth retardation was discernible at 26 wk, compared to controls. Over 80% of the animals died between weeks 17 and 35. Hematology and urine components were within the normal range except for high blood non-protein nitrogen in males. Upon necropsy, hypertrophied uteri, ovaries, seminal vesicles and hypertrophied stomachs, occasional ulcers, bloody mucus in the intestinal tract, and bronzed kidneys and livers were observed. Abnormal hepatic and renal changes, varying degrees of testicular damage, and a marked depression in tissue storage of iron was also observed. Chronic exposure to 1.14% Copper Gluconate in the diet was considered toxic.	27,28

Table 4. Repeated dose toxicity studies on Copper Gluconate

Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
feed	Male and female Beagle dogs (6/group/sex)	Up to 1 yr (52 wk)	0.012, 0.06, or 0.24% in the diet (equivalent to 3, 15, or 60 mg/kg/d)	Clinical chemistry parameters and urine samples were obtained at 4, 13, or 26 wk. Interim sacrifice and necropsy of 2 animals/sex/group was performed after 6 mo of treatment . No further details were provided.	After 6 mo of dosing, no differences were noted in overall health, hematology, urinalysis, food consumption, or body weight gain, between test animals and controls. After 1 yr of dosing, 1 out of 12 dogs from the 0.24% group exhibited minimal liver function, which was reversible with a 12-wk withdrawal period. No test-article related deaths occurred and gross or microscopic pathologic lesions were not observed upon sacrifice. Accumulation of copper was seen in the liver, kidneys, and spleen in the 0.24% group; no other test article-related effects were observed at the lowest dose or in any dog.	27,28
drinking water	Male C57BL/6J mice (number not specified)	animal lifetime	1st experiment: 0.005 M Copper Gluconate (317 ppm copper) in ~ 4 ml water/d) 2nd experiment: 0.0005 or 0.001 M Copper Gluconate (12.7 or 63.5 ppm copper)	Mice also received copper in the diet ad libitum (incidentally containing 18 ppm copper in the ash) from the beginning of the study; controls received distilled water, ad libitum 1st experiment: mice received Copper Gluconate in drinking water from 58 d of age. 2nd experiment: mice received Copper Gluconate in drinking water from 31 d of age.	Survival curves and lifespan were significantly reduced by14.4% (0.005 M; $p < 0.01$) for treated mice in the 1st experiment and by 11.8% (0.0005 M; $p > 0.05$) and 14.7% (0.001 M; $p < 0.01$) for mice in the 2nd experiment. These results indicated the absence of dose-response relationship for survival. Animals that consumed Copper Gluconate weighed slightly less than controls throughout the experiment.	22
Cow milk infant formula	Young Capuchin monkeys (2/sex) -treated group -age-matched controls	3 yr (156 wk)	3.5 mg/d, increased to 5.5 mg/d (of copper, as Copper Gluconate) over initial 2 mo	Newborn monkeys received a daily Copper Gluconate dose in formula, adjusted to the monkey's body weight every 2 wk, even after fruits and vegetables were introduced to the diet at 4 - 6 mo. Blood samples were collected every 2nd month during the 1st year and every 3rd month thereafter. Hematological indicators, liver aminotransferases (serum aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase), and serum and hair copper concentrations were measured. The liver was biopsied every 3rd month during the 1st year and every 6 mo thereafter, to assess general hepatic structure and visualize copper distribution.	No differences in food intake or body weight were observed, including weight gain by age or time of exposure, between the treated animals and controls. Gamma glutamyl-transpeptidase was significantly greater in treated animals compared to controls; no differences were observed in the other hematological indicators or liver aminotransferases. At 24 mo, levels of the antibodies Ki67 and MT1 in liver tissue were greater in treated animals compared to controls. After 36 mo, copper hair and liver concentrations were significantly greater in treated animals (4 -5 times that of controls).	29
In food (fruits or sauces)	Adult tufted Capuchin monkeys - treated group (2/sex) - age-matched controls (3 males/1 female)	3 yr (156 wk)	5 mg/d, increased to 7.5 mg/d (of copper as Copper Gluconate) over initial 2 mo	The monkeys were 3 - 3.5 yr old at enrollment. Blood, hair and liver samples were collected and analyzed as described above. At the end of the experiment, liver biopsies were assessed for the relative abundance of 4 transcripts encoding proteins related to copper uptake, storage and metabolism (*MT2a*, *APP*, *DMT1*, and *CTR1*) and 3 proteins related to hepatic responses to injury (*HGF*, *TGFβ*, and *NFκB*).	No differences in food intake or body weight were observed between the treated animals and controls. Hemoglobin and mean corpuscular volume were significantly lower and free erythrocyte protoporphyrin was significantly greater in treated animals compared to controls; liver aminotransferases did not differ between groups. At 24 mo, levels of Ki67 and MT1 proteins in liver tissue were significantly greater in treated animals compared to controls. When assessed after 36 mo, the hepatic mRNA expression of *NFκB*, *HGF*, and *TGFβ* was significantly greater in the treated animals, compared to controls, with no further evidence of clinical, hematological, or histological evidence of liver damage. Copper hair and liver concentrations were significantly greater (4 - 5 times that of controls) in treated animals.	29

Table 4. Repeated dose toxicity studies on Copper Gluconate

Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
COMPUTATIONAL						
NA	NA	NA	NA	Results from a QSAR model (described in an ECHA dossier); based on REACH guidance QSARs R.6 and were used to predict the oral LOAEL for Copper Gluconate in rats.	LOAEL = 94.7 mg/kg bw/d (oral) According to this value and the GHS/CLP classification, the STOT RE -2 designation, indicating presumed toxicity to specific organs with repeated exposure, was considered applicable.	3

Table 5. Developmental and reproductive toxicity studies on Copper Gluconate

Vehicle	Animals/Group	Dose	Procedure	Results	Reference
ORAL					
Distilled water	Male albino rats (8/group)	3.75, 7.5, or 15 mg/kg/d	Animals were dosed via gavage for 90 d. Two control groups received either 1 ml of saline or 0.5 ml DMSO for the duration of the study. Several antioxidant enzymes activities in the testis tissue of rats were determined spectrometrically.	Copper Gluconate did not significantly affect catalase levels but did significantly reduce glutathione and superoxide dismutase levels (at the medium and high dose), while increasing malondialdehyde levels, compared to controls. These findings are indicative of the development of oxidative stress.	30
Not specified	Female Swiss-Webster mice (20/group)	0, 0.1, 3, 30 mg/kg/d	The test article was administered, via gavage, to pregnant mice on days 6 to 14 of gestation.	Neither embryotoxic nor teratogenic. The average length and weight of the fetuses, their number per litter, and the incidence of skeletal and soft tissue abnormalities did not differ in test animals as compared to controls.	27,28
Not specified	Female albino Wistar rats (number not specified)	0, 0.1, 3, 30 mg/kg/d	The test article was administered, via gavage, to pregnant rats on days 5 to 15 of gestation.	Neither embryotoxic nor teratogenic. Weekly body weights and food intake were similar among all groups. Corpora lutea, implantation sites, implantation loss were not affected by treatment. The mean number of fetuses/litter, fetal viability, and resorption sites in the treated groups did not differ from the control group. Measurements of fetal weight and length as well as incidence of skeletal and soft tissue abnormalities were also unaffected by treatment.	27,28
Not specified	Male and female Wistar rats (males: 10/group; females: 20/group)	Female rats: 0, 3, or 30 mg/kg/d Male rats: 0 or 3 mg/kg/d	Female rats were dosed (via gavage) with Copper Gluconate 15 d prior to mating with untreated males, during gestation, and for 21 d postpartum. Two groups of male rats were treated 60 d prior to mating (via gavage). One group of treated males was mated with untreated females and the 2nd group of treated males was mated with females who had also received 3 mg/kg/d Copper Gluconate 60 d prior to mating. A third group of untreated males mated with untreated females served as controls.	Male rat reproductive performance was not affected by Copper Gluconate. No significant differences were observed between the percentage of pregnancies, the number and distribution of embryos in each uterine horn, implantation sites, resorption sites, duration of gestation, mean number of fetuses and live pups per litter, litter size, stillborn and live born numbers, gross anomalies and mean weight per pup, compared to controls. At the end of the 21-d postpartum period, necropsies of the dams and pups from all groups revealed a lack of visceral abnormalities. Under the conditions of this study, the researchers concluded that Copper Gluconate did not affect the reproductive performance of either male or female rats.	27,28
COMPUTATIONAL					
NA	NA	NA	As described in an ECHA dossier, an oral NOAEL reproductive toxicity in rats was determined using a QSAR model following the REACH Guidance on QSARs and Grouping of Chemicals R.6. However, the specifics of how these values were derived were not provided.	NOAEL = 318 mg/kg bw/d	3
NA	NA	NA	as above, but for developmental toxicity in rats	NOAEL = 793 mg/kg bw/d	3

Table 6. Dermal irritation and sensitization studies

Test Article	Vehicle	Dose	Test Population	Protocol	Results	Reference
HUMAN REPEATED-INSULT PATCH TESTS						
Leave-on baby product containing 0.00008% Copper Gluconate	applied neat	0.2 ml/mg Copper Gluconate dose applied: 0.00004 mg/cm^2	210 subjects	HRIPT; occlusive conditions (patch size 4 cm^2); 9 induction patches; challenge patch was applied to an untreated site after 2 wk. Challenge readings were taken 24, 48, 72, and 96 h after patch removal.	non-irritating; non-sensitizing	33
Rinse-off adult product containing 0.00008% Copper Gluconate	applied neat	0.2 ml/mg Copper Gluconate dose applied: 0.00004 mg/cm^2	211 subjects	HRIPT; occlusive conditions (patch size 4 cm^2); 9 induction patches; challenge patch was applied to an untreated site after 2 wk. Challenge readings were taken 24, 48, 72, and 96 h after patch removal.	non-irritating; non-sensitizing	34
Powder containing 0.1% Copper Gluconate	distilled water	0.1 – 0.15 g Copper Gluconate dose applied: 0.025 – 0.038 mg/cm^2 (equivalent to 0.0036 – 0.0054 mg/cm^2 copper)	52 subjects	HRIPT; occlusive conditions; 9 induction patches (~0.025 – 0.038 mg/cm^2 of test material per patch); challenge patch was applied to an untreated site after ~ 2 wk. Challenge readings were taken 24 and 72 h after patch removal.	non-irritating; non-sensitizing	35
Rinse-off baby product containing 0.2% Copper Gluconate	applied neat	0.2 ml/mg Copper Gluconate dose applied: 0.1 mg/cm^2	217 subjects	HRIPT; occlusive conditions (patch size 4 cm^2); 9 induction patches; challenge patch was applied to an untreated site after 2 wk. Challenge readings were taken 24, 48, 72, and 96 h after patch removal.	non-irritating; non-sensitizing	36
COMPUTATIONAL						
Copper Gluconate	NA	NA	NA	Results from a QSAR model (described in an ECHA dossier) are based on REACH guidance and were used to predict a PDII of 2.26 in rabbit skin.	Prediction of being non-irritating and non-sensitizing	3
Copper Gluconate	NA	NA	NA	Results from a QSAR model (described in an ECHA dossier) were used to predict that the EC3 for Copper Gluconate in a local lymph node proliferative assay is 5.08%.	Based on an EC3 value > 2%, Copper Gluconate was classified as having low to moderate skin-sensitizing potential (Skin Sensitizer Category 1B, under GHS category 1)*	3

*substances that show a low to moderate frequency of occurrence in humans and/or low to moderate potency in animals and can be presumed to potentially produce significant sensitization in humans.

Table 7. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	Reference
				IN VITRO		
Face cream containing 0.0025% Copper Gluconate	applied neat	100 µl	EpiOcular™ tissues, tested in duplicate	Tissues were treated for 4, 8, 16 and 24 h in a MTT assay. 0.3% Triton X-100 and distilled water served as positive and negative controls, respectively. Because the treatment with the test article reduced MTT in the absence of viable tissue, a killed control experiment was conducted. Little or no direct MTT reduction was observed in test article-treated killed controls compared to negative controls with killed cells; MTT reduction in the test article-treated viable tissue was ascribed to the viable cells.	ET_{50} > 24 h (compared to 24 min for the positive control); classified as minimally or not irritating Cell viability after each treatment time: After 4 h: 111.1% 8 h: 107.2% 16 h: 92.2% 24 h: 63.7%	38
				COMPUTATIONAL		
Copper Gluconate	NA	NA	NA	Using QSAR Toolbox 3.4.0.17 and REACH guideline on QSAR, the MMAS for Copper Gluconate was predicted in rabbit eyes.	MMAS = 49.5 Copper Gluconate predicted to be mildly toxic, considering the maximum value for damage to the cornea, conjunctiva, and iris is 110. Based on GHS criteria, Copper Gluconate was classified as a possibly mild irritant to the eyes (Category 2B).	3

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