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# Safety Assessment of Inositol as Used in Cosmetics

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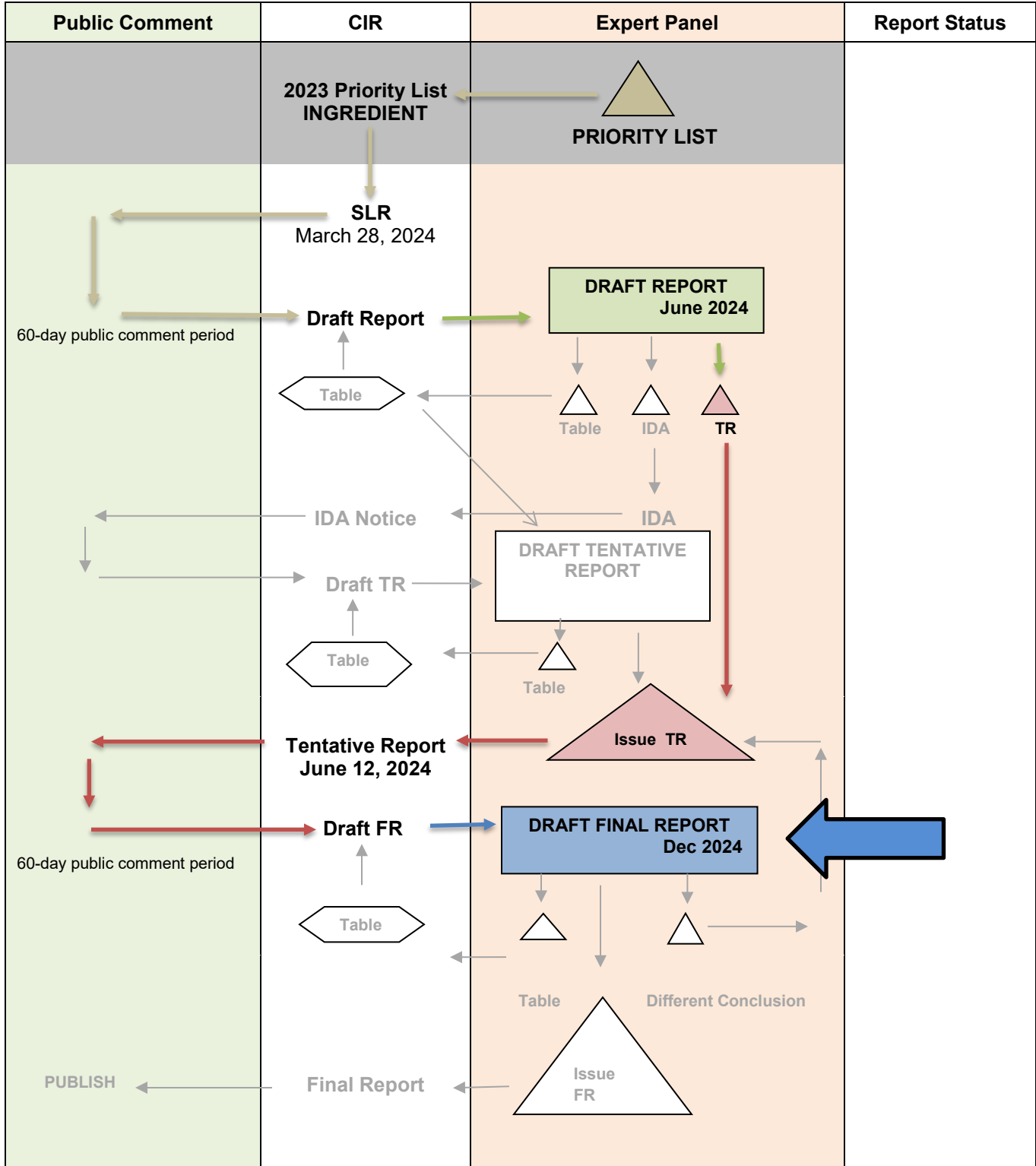
Status: Draft Final Report for Panel Review  
Release Date: November 8, 2024  
Panel Meeting Date: December 2 – 3, 2024

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; 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 Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR.

# SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Inositol

MEETING December 2024





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### **Memorandum**

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons  
From: Priya Cherian, MS, Senior Scientific Analyst/Writer, CIR  
Date: November 8, 2024  
Subject: Safety Assessment of Inositol as Used in Cosmetics

Enclosed is the Draft Final Report on the Safety Assessment of Inositol as Used in Cosmetics (*report\_Inositol\_122024*). Comments on the Tentative Report were received (*PCPCcomments\_Inositol\_122024*). Responses to these comments are included in this packet as *response-PCPCcomments\_Inositol\_122024*.

Additional supporting documents included in this packet include:

- flow chart (*flow\_Inositol\_122024*)
- report history (*history\_Inositol\_122024*)
- search strategy (*search\_Inositol\_122024*)
- a data profile (*datapofile\_Inositol\_122024*)
- transcripts (*transcripts\_Inositol\_122024*)

It should be noted that updated concentration of use data have been received from Council (*data\_Inositol\_122024*). This ingredient is now reported to be used at up to 4% in face and neck preparations. It was previously reported to be used at up to 2% in this product category in 2022. In addition, 2024 Registration and Listing Data (RLD) have been included in the report, alongside 2023 FDA VCRP data. Inositol is reported to be used in 212 and 1167 total formulations according to VCRP data and RLD, respectively.

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



## Memorandum

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

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

**DATE:** July 3, 2024

**SUBJECT:** Tentative Report: Safety Assessment of Inositol as Used in Cosmetics (release date June 12, 2024)

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

Abbreviations – ED<sub>5</sub> is not found in the report and can be deleted. If it really is a “median”, “5” should be “50”.

Introduction – Consider adding that phosphorylated inositol, Phytic Acid, Sodium Phytate, Phytin and Trisodium Inositol Phosphate) have been reviewed by CIR and found safe as used (final report 2018).

It would be helpful to note that the information on the ECHA website is on myo-Inositol.

Chemical Properties – Please correct “Other chemical properties of Inositol (both myo-inositol and D-chiro-inositol) be found in Table 1.” (either add the word “can”, or change “be” to “are”)

Method of Manufacture – If the information about phosphorylated inositol is not added to the Introduction, it would be helpful to describe what “phytate” is in the Method of Manufacture section.

Non-Cosmetic Use – It should be noted that everything listed in the FDA database as containing Inositol as an "active" is either listed as a dietary supplement, unapproved drug other (the veterinary drugs) or unapproved homeopathic drug.

Developmental and Reproductive Toxicity – It is not clear what happened to estrus cycles in the Inositol treated mice. It says: “cycles were arrested at day 8-10 in treated mice of all at all concentrations and in positive controls.” Since mg/kg doses are stated rather than concentrations, it would be clearer if it said, “at all doses of Inositol” (if this is correct). Please

correct “of all at all”.

Developmental and Reproductive Toxicity, Other – Please correct: “phosphorlayed” to “phosphorylated”

Anti-carcinogenicity – How the mice were treated, e.g., dietary or drinking water, should be stated.

Clinical Studies, Effect of Inositol on Reproductive Dysfunction – Was there any information about the dose/concentration of Inositol included in the suppositories?

Summary – In the Summary, the description of the DART study in which female rats were treated with 1% Inositol, please state that this was a dietary treatment.

In the description of the guinea pig maximization study in the Summary it says: “determined to be non-sensitizing in a guinea pig maximization assay (intradermal injection induction: 10 - 20% Inositol; intracutaneous induction....” . Intradermal and intracutaneous mean the same thing. The second route of treatment should be epicutaneous or dermal.

The Summary should not state “idiopathic couples”. The infertility of the couples was idiopathic.

Discussion – Since there is only one ingredient in this report, “from these ingredients” needs to be corrected to “from this ingredient”

Table 3, reference 18 – Since only group 1 had measurements at time points less than 1 hour, the following sentence should be revised to indicate that it only applies to group 1 animals, not all the test animals. “The highest mean Inositol concentration in serum samples was observed within the first hour after administration in all test animals.”

Table 3, reference 79 – Please correct: “except at day 72 d” (delete “d”, or “day”)

Table 4, second row, test system column – The first *S. cerevisiae* needs to be corrected to *S. typhimurium* (only D4 is an *S. cerevisiae* strain).

<b>Inositol – December 2024 – Priya Cherian</b>	
<b>Comment Submitter: Personal Care Products Council</b>	
<b>Date of Submission: July 3, 2024</b>	
<b>Comment</b>	<b>Response/Action</b>
Abbreviations – ED5 is not found in the report and can be deleted. If it really is a “median”, “5” should be “50”.	Addressed
Introduction – Consider adding that phosphorylated inositol, Phytic Acid, Sodium Phytate, Phytin and Trisodium Inositol Phosphate) have been reviewed by CIR and found safe as used (final report 2018).	Addressed
It would be helpful to note that the information on the ECHA website is on myo-Inositol.	Addressed
Chemical Properties – Please correct “Other chemical properties of Inositol (both myo-inositol and D-chiro-inositol) be found in Table 1.” (either add the word “can”, or change “be” to “are”)	Addressed
Method of Manufacture – If the information about phosphorylated inositol is not added to the Introduction, it would be helpful to describe what “phytate” is in the Method of Manufacture section.	Addressed
Non-Cosmetic Use – It should be noted that everything listed in the FDA database as containing Inositol as an "active" is either listed as a dietary supplement, unapproved drug other (the veterinary drugs) or unapproved homeopathic drug.	These uses were deleted from the report as they are no longer listed on the FDA website.
Developmental and Reproductive Toxicity – It is not clear what happened to estrus cycles in the Inositol treated mice. It says: “cycles were arrested at day 8-10 in treated mice of all at all concentrations and in positive controls.” Since mg/kg doses are stated rather than concentrations, it would be clearer if it said, “at all doses of Inositol” (if this is correct). Please correct “of all at all”.	Addressed
Developmental and Reproductive Toxicity, Other – Please correct: “phosphorlayed” to “phosphorylated”	Addressed
Anti-carcinogenicity – How the mice were treated, e.g., dietary or drinking water, should be stated.	Addressed
Clinical Studies, Effect of Inositol on Reproductive Dysfunction – Was there any information about the dose/concentration of Inositol included in the suppositories?	No
Summary – In the Summary, the description of the DART study in which female rats were treated with 1% Inositol, please state that this was a dietary treatment.	Addressed
In the description of the guinea pig maximization study in the Summary it says: “determined to be non-sensitizing in a guinea pig maximization assay (intradermal injection induction: 10 - 20% Inositol; intracutaneous induction....” . Intradermal and intracutaneous mean the same thing. The second route of treatment should be epicutaneous or dermal.	Addressed
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## **Inositol History**

### **August 2023**

- Communication with PCPC regarding which inositol configurations are used in cosmetic formulations – myo-inositol and d-chiro-inositol were determined to be the configurations sold in cosmetic products

### **March 2024**

- SLR posted

### **April 2024**

- Comments on SLR received from PCPC

### **June 2024**

- Panel reviews Draft Report and issues Tentative Report with public comment with safe as used conclusion

### **July 2024**

- Comments on Tentative Report received from PCPC

### **October 2024**

- Updated concentration of use data received; Inositol is now reported to be used at a maximum concentration of 4% (was previously reported to be used at up to 2% in 2022)

### **December 2024**

- Panel reviews Draft Final Report

**Inositol Data Profile\* - December 2024 - Writer, Priya Cherian**

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization			Ocular Irritation		Clinical Studies
	Reported Use	Method of Mfg	Impurities	log P/log K <sub>ow</sub>	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	Computational	In Vitro/In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal
<i>myo</i> -inositol	X	X	X	X		X				X			X						X				X				X
<i>D-chiro</i> -inositol		X		X		X				X																	X
inositol (isomer unspecified)													X														X

\* "X" indicates that data were available in a category for the ingredient

**Inositol**

CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
87-89-8; 643-12-9	x	x	x		x				x							x

**Search Strategy****PUBMED:**

- INCI name searched along with “Typical Search Terms” listed below
- CAS numbers searched
- Chemical/technical names searched
- Inositol configurations searched: cis-inositol, epi-inositol, allo-inositol, myo-inositol, muco-inositol, neo-inositol, D-chiro-inositol, L-chiro-inositol, scyllo-inositol

**Typical Search Terms**

- |              |                 |                    |
|--------------|-----------------|--------------------|
| ▪ metabolism | ▪ irritation    | ▪ manufacture      |
| ▪ dermal     | ▪ synthesis     | ▪ cancer           |
| ▪ inhalation | ▪ impurities    | ▪ safety           |
| ▪ skin       | ▪ ocular        | ▪ mutagenicity     |
| ▪ toxicity   | ▪ eye           | ▪ genotoxicity     |
| ▪ drug       | ▪ sensitization | ▪ pharmacokinetics |
| ▪ medicine   | ▪ allergy       | ▪ topical          |

**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/oppt/hpv/public\\_search.html\\_page](https://iaspub.epa.gov/oppt/hpv/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_en) [https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs\\_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](http://www.google.com) <https://scholar.google.com/>

**JUNE 2024 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT****Belsito Team – June 3, 2024**

**DR. BELSITO:** Okay. Inositol was another one that we got a bunch of Wave 2 on. Is everyone okay? Does anyone need to a bio break?

**DR. KLAASSEN:** This is the last chemical.

**DR. BELSITO:** This is the last one. Yeah, the cocoyl hydrolyzed collagen, Bart has for you if you weren't here when we discussed that re-review. All right, maybe that's not you. I don't know. Anyway, Bart has that data, yes. So, this is our last one.

Okay. So, this is the first time we're looking at the review of this safety ingredient. It's a sole ingredient. First of all, with method of manufacture, is anyone concerned about bacterial contamination in the final product given the method of manufacture, microbial fermentation?

**DR. RETTIE:** Is that the new method of manufacture? It's not just one out of a bunch?

**DR. BELSITO:** Yeah, but it is one. I mean, so are you concerned? Is it something that we would need to put in a discussion when we get to writing a discussion on this report?

**DR. SNYDER:** My assumption was they would use standard manufacturing procedures that would minimize that or eliminate that.

**DR. BELSITO:** But that would be in a discussion.

**DR. SNYDER:** Yes.

**DR. BELSITO:** Okay.

**DR. RETTIE:** Yeah, I guess I was just assuming it the same deal as the yeast, at the end of the day (inaudible).

**DR. BELSITO:** Well, the yeast are killed.

**DR. RETTIE:** Yeah.

**DR. BELSITO:** So, just GMP to prevent, right, Paul?

**DR. SNYDER:** Yes, that's what I would have on it, Don, in the absence of somebody providing us that that's what they do.

**DR. BELSITO:** So, two percent max leave-on, one percent ocular. I was not concerned with systemic absorption; it was trivial. I have a note. What do you make of this need to put argument in discussion? This was, oh, the DART effect, Paul, on the ovaries.

**DR. SNYDER:** Tell me what page you're on.

**DR. BELSITO:** PDF Page 18.

**DR. SNYDER:** I didn't have anything in my notes.

**DR. RETTIE:** (Inaudible) same absorption (inaudible) so your first comment, absolutely correct. Then I noted that there are - you know a little more about this, Curt, than me -- sugar transporters. And at least after any kind of uptake from oral ingestion (inaudible) we have sugar transporters. Would that have a bearing on some of this?

**DR. KLAASSEN:** Well, we definitely have glucose transporters. If, quote, this glucose-type compound is absorbed by the glucose transporter, I don't know.

**DR. BELSITO:** But given the level of use and given the natural and ingested sources of inositol, are you concerned about that, Allan?

**DR. RETTIE:** I guess not since it's GRAS (inaudible). Just wanted to hear transport from Curt.

**DR. KLAASSEN:** Yeah, I don't know specifically about this compound.

**DR. BELSITO:** Okay.

**DR. RETTIE:** You're right. It's not real sugar.

**DR. KLAASSEN:** No, it's a (inaudible).

**DR. RETTIE:** (Inaudible).

**DR. BELSITO:** We also got Wave 2 on lack of vaginal mucosal irritation. We have it in use three percent face cream for five weeks, negative. We had a read-across to phytic acid, which I thought was fine, with HRIPTs. We had some guinea pig maximization tests.

So, my final read on this was safe as used. It's GRAS and endogenous. We have in vitro DART effects that were, I thought, irrelevant, secondary to the dose. Genotox was okay. In silico, limited Ames, in GRAS status, respiratory boilerplate, negative irritation data, okay with limited sensitization, in-use test, given use test on phytic acid.

**DR. RETTIE:** The only thing that caught my eye within that was for the increased allergens and decreased estrogen (inaudible). Is that something we need to be thinking about?

**DR. BELSITO:** That was in the DART. That's what I asked Paul about, that we need to discuss that. I think it's a dose effect, right?

**DR. SNYDER:** Yeah, I think it's fine. I think with the GRAS test and the nature of this I don't think we have anything to consider about.

**DR. RETTIE:** I was just surprised to read it.

**DR. KLAASSEN:** Yeah, that was a little surprising I thought too.

**DR. BELSITO:** Give enough water intratracheal, people die.

**DR. KLAASSEN:** On Page 21 in the summary, where it gives the predicted acute oral LD50, is 19,483.68 milligrams per kilogram. Can we change that to 19.5 grams?

**DR. BELSITO:** I don't know, Curt. That's not what the data said.

**DR. KLAASSEN:** The computer was wrong.

**DR. BELSITO:** Okay. So, is --

**DR. RETTIE:** You know that they may include those just to get you riled up.

**DR. BELSITO:** So, is everyone okay with safe as used?

**DR. SNYDER:** I am.

**DR. RETTIE:** Yes.

**DR. BELSITO:** Okay. Discussion. Good manufacturing to prevent bacterial contamination. DART effect. Irrelevant dose to cosmetics. GRAS status. Endogenous production. Respiratory boilerplate. That's the discussion. Okay. Anything else.

Carol, were you going to say something?

**DR. EISENMANN:** No.

**DR. BELSITO:** Anyone want to say anything?

**DR. RETTIE:** (Inaudible).

**DR. BELSITO:** If not, I can't believe the Cohen team beat us. Okay.

**DR. KLAASSEN:** (Inaudible).

**DR. BELSITO:** I am not turning off my computer tonight because --

**MS. FIUME:** Is that yours?

**DR. BELSITO:** This is mine. It finally opened up because Kevin's computer wiped out my thumb drive. Wiped out. I don't know how it did it. It wiped out all the comments on my thumb drive. So, I've reloaded my thumb drive off of my computer. I'm working off of my thumb drive, but --

**MS. FIUME:** (Inaudible).

**DR. BELSITO:** I was able to reload them. I was able to get on my computer, reload my thumb drive, and I've been working off my thumb drive. But I can't use Kevin's computer tomorrow because I don't want all of my comments to be erased again. I don't know why they erased them. I don't have a clue. It saved the first two I was working off his computer on. And then when I went to open up the paraphenylenediamine document, I had no comments. And when I looked at --

### Cohen Team – June 3, 2024

**DR. COHEN:** Inositol. This is a draft report on the safety assessment of inositol. It's the first time we're seeing this. It should be noted that there are nine potential geometric isomers of inositol and according to the dictionary two isomers used in

the production of cosmetic ingredients are myo-inositol and D-chiro-inositol. Data on both of these configurations have been included in the report. Inositol's reported to function as a hair conditioning agent and humectant.

It's a ubiquitous substance found in organisms, and it may be found as a free sugar alcohol or as a head group of membrane lipids. According to the 2023 VCRP, inositol's used in 212 total formulations, most of which are leave on and some are rinse off. The concentration of use survey by the Council in 2022 indicate that inositol is used up to 22 percent in face and neck and moisturizing products. Ocular exposure to inositol may occur and it's used near the eye in an eye lotion up to one percent.

We have sensitization data at max use; we have irritation data as well. I'll just open it up to the group for comments.

**DR. BERGFELD:** I think it's important to say it's animal sourced. That's what they said in the document that -- because that comes into the discussion.

**DR. ROSS:** That's a good point. I didn't catch that, actually.

**DR. COHEN:** But it says in method of manufacturing it's produced by hydrolysis microbial fermentation and -- there's a microbial fermentation for it in method of manufacturing.

**DR. BERGFELD:** I don't know. I read that the basic ingredient was from liver and kidneys in animals, then it was treated.

**DR. COHEN:** Let me go back to method of manufacturing. Hydrolysis, microbial fermentation, in vitro enzymatic biocatalyst. I don't see --

**DR. BERGFELD:** It's a GRAS item.

**DR. COHEN:** It's a GRAS item. It's GRAS but I don't see the animal source in method of manufacturing.

**DR. TILTON:** It's not listed here.

**DR. BERGFELD:** Not listed there? Unless I can find it. I wrote it down because I know it was important.

**MS. FIUME:** It's under the dictionary; it's a plant and synthetic source.

**DR. BERGFELD:** A synthetic?

**MS. FIUME:** In the dictionary.

**DR. BERGFELD:** Okay. Well, somewhere I picked it up. Let me -- okay. Sponge that.

**MS. FIUME:** You can find it for us. If you happen to see it and we'll look for it as well.

**DR. BERGFELD:** I wrote it down because I saw it. Wait a minute.

**DR. COHEN:** There's like 53 notes of animal in the report but --

**DR. BERGFELD:** Well, go on. Don't -- I'll look for it.

**DR. ROSS:** We'll come back. Wilma's usually right.

**DR. COHEN:** That's a fact. So, what are your comments on it? Susan, you want to go?

**DR. TILTON:** Well, because it's a food additive with GRAS status, systemic exposure's really of low concern. Although the data that was provided show that there were no effects, or no acute short-term oral toxicity, no repro or developmental effects, predicted to be non-genotoxic in vitro and by QSAR. You discussed some of the dermal sensitization/irritation data. Non-sensitizing in the guinea pig maximization test at a hundred percent. A non-irritant in the EpiOcular studies at up to 50 milligrams.

And no irritation in the guinea pig test up to 0.1 grams. It's also been used in clinical studies with no evidence of safety concerns at higher doses. So, generally I had no concerns based on the toxicity data that was provided.

**DR. COHEN:** Yeah. You had a safe as used?

**DR. TILTON:** Safe as used.

**DR. COHEN:** David?

**DR. ROSS:** Yeah. Acute tox, DART, genotox, okay. Anti-carcinogenic, non-irritating, sensitization looks good. As Susan pointed out, the ocular looked good in (inaudible) in the EpiOcular studies. I came up with safe as used.

**DR. COHEN:** We've harmonized our findings.

**DR. BERGFELD:** It's interesting because we used this as a food additive in hair loss.

**DR. COHEN:** Is that right?

**DR. BERGFELD:** It mimics metformin.

**DR. COHEN:** Just a procedural question. When is lunch officially?

**MS. FIUME:** It typically starts at noon.

**DR. COHEN:** Starts at noon.

**MS. FIUME:** It could be whenever.

**DR. COHEN:** Do you want to do one more.

**DR. ROSS:** Yeah.

**MS. FIUME:** Before we go on, so that I have it, do you have any discussion items that you have specifically?

**DR. COHEN:** I didn't have anything particular in the discussion. I'll have to think about it tonight. It was a very straightforward, wonderfully written report.

**DR. BERGFELD:** I think you could bring out the GRAS.

**DR. COHEN:** I like that, thank you. Thank you.

**MS. FIUME:** And that the data are sufficient.

**DR. BERGFELD:** And the data are sufficient.

**MS. FIUME:** And relevant. Wilma, I found what you're looking for. It's the last two sentences under natural occurrence on PDF page 16. It's just pointing out what animal tissues are richest in inositol because it's ubiquitous in living organisms.

**DR. BERGFELD:** Okay. Thank you.

**DR. COHEN:** So, if you wanted to eat it, you can, right? From those sources? Hold on one second.

#### **Full Panel – June 4, 2024**

**DR. BELSITO:** Okay, so this is actually the first time that we're looking at the data on this ingredient. It is both GRAS and it is endogenously produced. It gave us some comfort in terms of systemic toxicities. Having looked at all of the data that we got and the comments from PCPC in the second wave, which we agreed with, we thought that we could go with a safe as used conclusion for this.

**DR. COHEN:** Second.

**DR. BERGFELD:** Second. Any further discussion regarding this ingredient? Seeing none, call the question, all those in favor please raise your hand. Thank you.

**DR. SNYDER:** I concur.

**DR. BERGFELD:** Unanimous, thank you. All right, going on to the next ingredient, looks like it's 4-Chloro-2-Aminophenol, Dr. Cohen.

## **Safety Assessment of Inositol as Used in Cosmetics**

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Status: Draft Final Report for Panel Review  
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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; 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 Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR.

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**ABBREVIATIONS**

ADME	absorption, distribution, metabolism, and excretion
BMI	body mass index
C <sub>max</sub>	maximum observed plasma concentration
CAS	Chemical Abstracts Service
CFU	colony-forming units
CIR	Cosmetic Ingredient Review
CLP	classification, labeling, and packaging
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
<i>Dictionary</i>	web-based <i>International Cosmetic Ingredient Dictionary and Handbook</i>
DMSO	dimethyl sulfoxide
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
ET <sub>50</sub>	exposure time which reduces MTT reduction by 50%)
EU	European Union
FCA	Freund's complete adjuvant
FDA	Food and Drug Administration
FOU	frequency of use
HESS	Hazard Evaluation Support System
HET-CAM	hen's egg test chorioallantoic membrane
HRIPT	human repeated insult patch test
LD <sub>50</sub>	median lethal dose
log K <sub>ow</sub>	n-octanol/water partition coefficient
MMP	mitochondrial membrane potential
MoCRA	Modernization of Cosmetics Regulation Act
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
NR	none reported
OECD	Organisation for Economic Cooperation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PKB	protein kinase B
QSAR	quantitative structure-activity relationship
RLD	Registration and Listing Data
T <sub>max</sub>	time to peak concentration
TG	test guideline
VCRP	Voluntary Cosmetic Registration Program

## **ABSTRACT**

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Inositol, which is reported to function in cosmetics as a hair-conditioning agent and humectant. The Panel reviewed the available data to determine the safety of this ingredient. The Panel concluded that Inositol is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

## **INTRODUCTION**

This assessment reviews the safety of Inositol as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook (Dictionary)*, Inositol is reported to function in cosmetics as a hair-conditioning agent and humectant.<sup>1</sup>

Inositol is commonly consumed<sup>2</sup> and is generally recognized as safe (GRAS) in the US for use as a direct food additive and dietary supplement [21CFR184.1370 and 21CFR582.5370]. Daily exposure from food use would result in much larger systemic exposure than those from cosmetic products; therefore, the primary focus of this safety assessment on Inositol as used in cosmetics is the potential for local effects from topical exposure.

Various polyol phosphates including phytic acid, sodium phytate, phytin, and trisodium inositol phosphate, which are inextricably linked to Inositol, have previously been reviewed by Cosmetic Ingredient Review (CIR) (report finalized in 2018; available from CIR (<https://cir-reports.cir-safety.org/>)).<sup>3,4</sup> These ingredients were determined to be safe as used in cosmetics according to the present practices of use and concentrations as stated in that safety assessment.

It should be noted that studies were found in the literature evaluating the metabolism of Inositol administered via methods that would result in high amounts of systemic exposure (i.e., intravenous and intraperitoneal administration). These studies were not included in the report as the systemic exposure via topical administration of Inositol is expected to be much lower than these methods of administration. In addition, studies were found in the literature regarding the use of Inositol as an oral supplement for various diseases. While summaries regarding the efficacy of Inositol for the treatment of these diseases are not provided in this report, a brief summary of the adverse effects observed in these studies can be found in the Clinical Studies section of this report.

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 October 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.

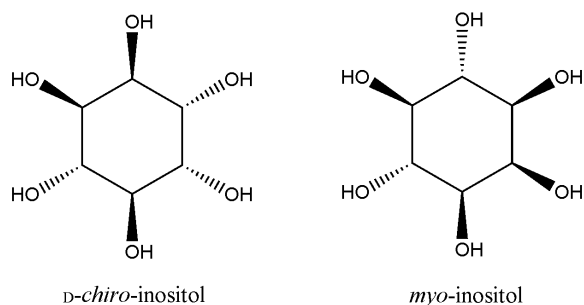
Inositol has 9 potential geometric isomers (see Chemistry section for further details). According to the *Dictionary*, the two isomers used as cosmetic ingredients are *myo*-inositol and *D-chiro*-inositol.<sup>5</sup> Therefore, data on the remaining 7 isomers have not been provided in this report, as they are unlikely to be used in cosmetics. In addition, when the isomer of Inositol used in studies presented throughout the report is known, the isomer-specific name will be identified (e.g., Inositol (as *myo*-inositol)), as appropriate. When the specific isomer is unknown, the terms “inositols” or “an inositol” will be used throughout report text, in lower-case letters, along with the notation “isomer unspecified,” in parenthesis.

Some of the data included in this safety assessment on *myo*-inositol were found on the European Chemicals Agency (ECHA) website.<sup>6</sup> 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**

Inositol (CAS No. 87-89-8; 643-12-9) is a cyclohexyl polyol containing 6 hydroxyl functional groups, 1 per cyclohexyl carbon.<sup>7</sup> Inositol has a structure that is similar to the cyclic form of pyranose sugars, such as glucose, but does not have an oxygen atom in the ring; thus, it is considered to be a sugar alcohol.<sup>5</sup> Inositol has 9 potential stereoisomeric forms, 6 of which are naturally-occurring (*myo*-, *D-chiro*-, *L-chiro*-, *muco*-, *scyllo*-, and *neo*-), and 3 of which are synthetic (*allo*-, *cis*-, and *epi*-). According to the *Dictionary*, Inositol is the cyclic polyol that conforms generally to the structures below (Figure 1), inclusive only of the *D-chiro*- (CAS No. 643-12-9) and *myo*-inositol (CAS No. 87-89-8) stereoisomers:



**Figure 1.** Inositol

### Chemical Properties

Inositol (as *myo*-inositol) is a white solid substance, with a water solubility of 28 g/100 g water (at 60 °C).<sup>6</sup> D-*chiro*-inositol has a molecular weight of 180.16 g/mol<sup>8</sup> and log  $K_{ow} = -2.60$ <sup>8</sup> and *myo*-inositol has a molecular weight of 180.16<sup>9</sup> g/mol and log  $K_{ow} = -2.08$ <sup>6</sup>. Other chemical properties of Inositol (both *myo*-inositol and D-*chiro*-inositol) can be found in Table 1.<sup>6,10,9,11,8</sup>

### Method of Manufacture

The following methods of manufacturing are general to the production of Inositol (both *myo*-inositol and D-*chiro*-inositol), and it is unknown whether these methods are used in the manufacture of Inositol for use in cosmetics.

Inositol (as *myo*-inositol) has been reported to be produced via hydrolysis, microbial fermentation, and in vitro enzymatic biocatalysis.<sup>12</sup> In conventional chemical acid hydrolysis, phytate is abstracted and purified via soaking, neutralization, and filtration. Phytate (an ester of *myo*-inositol) is hydrolyzed to produce *myo*-inositol via the use of inorganic acid under high temperature and pressure. Crude *myo*-inositol is concentrated and crystallized to produce refined *myo*-inositol. Modern hydrolysis production of *myo*-inositol includes the heating of a 40% aqueous solution of phytate with a catalyst consisting of glycerin, urea, and calcium carbonate. After a cooling period, the hydrolysate is cooled, filtered, crystallized, and washed to obtain refined *myo*-inositol.

For microbial fermentation, Inositol (as *myo*-inositol) is biosynthesized via the synergetic utilization of glucose and glycerol in *Escherichia coli*. In vitro cascade enzymatic biocatalysis involves the transformation of various substances (e.g., maltodextrin, amylose, starch, cellodextrins, sucrose, xylose) to *myo*-inositol with the use of several enzymes (e.g., maltodextrin phosphorylase, phosphoglucosmutase, inositol 1-phosphate synthase).

Inositol stereoisomers (such as D-*chiro*-inositol) can be prepared from *myo*-inositol by didehydroxylation.<sup>13</sup> D-*chiro*-inositol may also be synthesized from a chiral chloro-diol produced by dihydroxylation of chlorobenzene in the presence of *Pseudomonas putida* strain 39/D.<sup>14</sup> According to 21CFR184.1370, inositols, or *myo*-inositol, occurs naturally, and is prepared from an aqueous (0.2% sulfur dioxide) extract of corn kernels by precipitation and hydrolysis of crude phytate.

### Impurities

According to a supplier, Inositol (as *myo*-inositol) may not contain more than 50 mg/kg chloride, 100 mg/kg sulfate, 10 mg/kg heavy metals, 0.5 mg/kg arsenic, 0.5 mg/kg lead, or 5.0 mg/kg iron.<sup>15</sup> Microbial specifications indicate that Inositol (as *myo*-inositol) may not contain more 100 colony-forming units (CFU)/g total viable count, 100 CFU/g yeasts, or 100 CFU/g molds. The ingredient must also be negative for coliforms, *Escherichia coli*, and *Salmonella*.

According to the *Food Chemicals Codex* specifications, Inositol (as *myo*-inositol) must have a purity of  $\geq 97\%$ , with  $\leq 4$  mg/kg lead,  $\leq 0.005\%$  chloride, and  $\leq 0.006\%$  sulfate.<sup>16</sup> Purity information on Inositol (as *myo*-inositol) as a feed additive for fish, dogs, and cats has been provided by the European Food Safety Authority (EFSA).<sup>10</sup> Samples of Inositol (as *myo*-inositol) used as a feed additive were reported to have purities ranging from 99.3 - 99.9%. In addition, samples were reported to contain  $< 0.3\%$  D-mannitol,  $< 0.3\%$  propane-1,2,3-triol,  $< 0.5$  mg/kg lead,  $< 0.1$  mg/kg arsenic,  $< 0.01$  mg/kg cadmium,  $< 0.01$  mg/kg mercury, and  $< 0.128$  ng/kg dioxins and dioxin-like polychlorinated biphenyls.

### Natural Occurrence

Inositol is an ubiquitous substance found in living organisms that may be present as a free sugar alcohol or as a headgroup of membrane lipids.<sup>17</sup> Inositol plays an important role in several biological functions, such as maintaining metabolic homeostasis and cytoskeleton remodeling.<sup>18-20</sup> Of the 9 possible stereoisomers, *myo*-inositol is the predominant form of Inositol found in the human body; however D-*chiro*-inositol may also be found.<sup>21</sup> In addition, *myo*-inositol can be converted in the body to D-*chiro*-inositol via a nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate-dependent epimerase enzyme.<sup>22</sup> Animal tissues richest in Inositol (as *myo*-inositol) are the brain, heart, stomach, kidney, spleen, and liver.<sup>23</sup> In mammals, inositols are produced in the liver and kidneys at a rate of approximately 4 g/d.<sup>5</sup>

## 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). 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). Consequently, RLD are product-centric, whereas VCRP data were ingredient-centric. However, because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use.

According to 2023 VCRP survey data, Inositol is used in 212 total formulations (185 leave-on formulations and 27 rinse-off formulations; Table 2).<sup>24</sup> RLD collected in 2024 indicate that Inositol is used in 1167 total formulations.<sup>25</sup> The results of the concentration of use survey conducted by the Council in 2022 and updated in 2024 indicate Inositol is used at up to 4% (in face and neck products).<sup>26,27</sup>

Ocular exposure to Inositol may occur as this ingredient is used in products used near the eye (e.g., Inositol is used in eye lotion at up to 1%). In addition, mucous membranes are exposed and incidental ingestion may occur as Inositol is reported to be used lipstick formulations (concentration of use not provided). Inositol is also reported to be used in “other baby products”.

Inositol is used in a face powder formulation (concentration of use 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 this ingredient may be marketed for use with airbrush delivery systems; however, this information is not available from the VCRP, RLD, or the Council survey. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, 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 frequency and concentrations of use of this ingredient, and without consumer habits and practices data or particle size data related to this use technology, the Panel is not able to determine safety of this ingredient for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

Inositol is not restricted from use in any way under the rules governing cosmetic products in the European Union.<sup>28</sup>

### **Non-Cosmetic**

Inositol is used in several industries including food, medicine, and animal feed.<sup>29</sup> Inositol can be found in many foods, including vegetables, nuts, fruit, milk, grains, fish, meat, and eggs.<sup>30</sup> The amount of Inositol (as *myo*-inositol) present in a 2500 kcal American diet is approximately 900 mg.<sup>31</sup> Inositol is GRAS as a direct human food ingredient based upon current good manufacturing practice conditions of use [21CFR184.1370] and when used in animal nutrients and/or dietary supplements when used in accordance to good manufacturing or feeding practice [21CFR582.5370]. Inositol is used in infant formula in accordance with regulations listed in 21CFR105.65. This ingredient has been studied for use as treatment for many disorders including, but not limited to, plaque psoriasis, gestational diabetes mellitus, trichotillomania, mental health disorders, polycystic ovary syndrome, infertility, hypothyroidism, and non-alcoholic fatty liver disease.<sup>32-76</sup>

## TOXICOKINETIC STUDIES

### **Absorption, Distribution, Metabolism, and Excretion (ADME)**

Inositol (as *myo*-inositol) is actively transported by intestinal cells via sodium-ion coupled transporters.<sup>77</sup> The majority of the free Inositol is absorbed from the human gastrointestinal tract through this active transport system, after which it may reach body tissues via the bloodstream.<sup>78</sup> The cellular uptake and absorption of Inositol may be reduced or inhibited in the presence of glucose due to the competitive affinity for the same transporter system. Glucose may also deplete Inositol levels via the activation of the glucose-sorbitol pathway. Because of this, individuals with type 2 diabetes may display altered levels of Inositol excretion compared to healthy individuals.

Details regarding the studies summarized herein can be found in Table 3. More than 98% of total ingested Inositol (as *D-chiro*-inositol) was absorbed from the gastrointestinal tract in an assay in which rats were given a diet containing 0.23%

Inositol for at least 1 mo plus 1 wk.<sup>79</sup> Minimal amounts of the ingested Inositol were found in the feces and urine, suggesting extensive metabolism prior to excretion. The mean serum concentrations of 3 groups of rats given 2000 mg/kg Inositol (as *myo*-inositol) in distilled water were 54.4, 43.9, and 44.6 µg/ml (animals observed at different time intervals up to 24 - 48 h; highest concentrations observed within 1 h of administration).<sup>20</sup> Supplementation of the diet of pregnant rats with 0.5% Inositol (as *myo*-inositol) resulted in increased levels of Inositol in the plasma, liver, kidneys, and intestines of offspring, and increased levels of Inositol in the milk and mammary tissues of dams.<sup>80</sup> A maximum plasma concentration of 0.23 mM was observed in 8-d-old rats given a formula supplemented with 114 mg/100 ml Inositol (as *myo*-inositol; after 2 d of treatment).<sup>81</sup> In a study performed in 5 female subjects given 100 mg/kg bw Inositol (as *myo*-inositol) in water (oral ingestion), the highest urinary Inositol concentration was approximately 550 µmol/mmol creatinine 275 min after test substance administration.<sup>82</sup> The observed maximum serum concentration (96.5 µmol/l) was observed 90 min post-ingestion. Mean maximum observed plasma concentration ( $C_{max}$ ) values were similar in subjects administered oral doses of a soft gel containing 600 mg Inositol (as *myo*-inositol) and 2000 mg of Inositol (as *myo*-inositol) powder (mean  $C_{max}$  of 31.5 and 36.3 µmol/l, respectively).<sup>83</sup> Similarly, in the same study, mean  $C_{max}$  values were comparable following administration of a soft gel containing 1200 mg Inositol and 4000 mg of Inositol powder (mean  $C_{max}$  of 41.5 and 45 µmol/l, respectively). Maximum plasma concentrations in this study were observed 180 - 122 min after treatment.

## TOXICOLOGICAL STUDIES

### Acute Toxicity Studies

#### Animal

##### Oral

A median lethal dose (LD<sub>50</sub>) of 10 g/kg bw was determined for Inositol (as *myo*-inositol) in an acute oral toxicity assay performed in mice.<sup>6</sup> No details regarding this study were provided.

##### Computational

A quantitative structure activity relationship (QSAR) model (consensus model; Toxicity Estimation Software Tool v4.2.1) was used to evaluate the potential acute oral toxicity of Inositol (as *myo*-inositol) in rats.<sup>6</sup> The predicted acute oral LD<sub>50</sub> was determined to be 19.5 g/kg.

### Short-Term Toxicity Studies

#### Animal

##### Oral

The effect of Inositol (as *myo*-inositol) on weight gain and the patterns of lipids in the liver was evaluated in male Wistar rats (20-d-old and 3-mo-old; number of animals per group not stated).<sup>6</sup> Twenty-day-old rats received 10, 100, 200, or 1000 mg/kg bw/d and 3-mo-old rats were given 5, 50, 500, or 5000 mg/kg bw/d. Controls were used, but details regarding control animals were not provided. All administrations occurred for 45 d via gavage (water used as vehicle). No treatment-related effects on weight gain were observed in 3-mo-old rats compared to controls. In 20-d-old rats, growth was slightly inhibited in the 1000 mg/kg bw/d group, compared to controls. No significant differences in liver lipid patterns were observed in treated animals of either age compared to controls. No other details regarding this study were provided.

#### Human

##### Oral

Ten healthy women were supplemented with 1200 mg Inositol (as *D-chiro*-inositol), once per day, for 1 mo.<sup>84</sup> Clinical features were evaluated at baseline and after 1 mo of supplementation. After supplementation, statistically significant ( $p < 0.01$ ) increases in free testosterone levels and asprosin were observed. Differences between baseline and 1 mo post-treatment for all other parameters (body mass index (BMI), glycemia, insulinemia, insulin resistance, follicle-stimulating hormone, luteinizing hormone, estradiol, and dehydroepiandrosterone) measured were not statistically significant.

##### Computational

No alerts for short-term oral toxicity were raised for Inositol (as *myo*-inositol) in a Hazard Evaluation Support System Integrated Platform prediction using the QSAR Toolbox v4.1 (HESS Prediction v.2.9).<sup>6</sup> Similarly, Inositol (as *myo*-inositol) raised no alerts for organ toxicity following short-term oral exposure when evaluated computationally (Derek Nexus 5.0.2, Nexus 2.1.1).

## DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

#### Animal

##### Oral

The effect of Inositol (as *D-chiro*-inositol) on estrus cycles, ovary histology, serum testosterone, and ovarian aromatase was evaluated in female C57BL/6N mice (5/group).<sup>85</sup> Animals were given drinking water containing Inositol (5, 10, or 20 mg/d) for 21 d. A negative control group was given plain water, and a positive control group was given drinking water containing 0.5 mg/kg/d letrozole (a +estrogen-reducing agent). Starting from the second week of treatment, mice were subjected to daily evaluations of the progression of their estrus cycles via vaginal smears. At the end of treatment, animals

were killed and analyses were performed. Estrus cycles progressed through all phases in the negative control group; however, cycles were arrested at day 8 - 10 in treated mice at all doses of Inositol and in positive controls. No abnormalities were observed regarding the gross morphology of uteri/ovaries or histology following treatment in negative control animals. Uteri of mice that received either Inositol or letrozole displayed immature/metestrus-diestrus-like aspect and small/immature ovaries. Ovaries from mice treated with 5 mg/d Inositol had normal primary and secondary follicles, but had cystic tertiary follicles. Ovaries of letrozole-treated mice were similar, but contained larger cystic follicles, characterized by the absence of the oocyte. Ovaries of animals treated with 10 or 20 mg/d Inositol had some primary and secondary follicles, a very limited number of tertiary follicles, no follicles at more advanced stages, and no cystic follicles. In addition, animals treated with 10 or 20 mg/d Inositol displayed areas with diffused, aberrant cell proliferation. Levels of serum testosterone in the 5 mg/d treated group was statistically significantly increased compared to negative control mice ( $p < 0.05$ ). Levels of serum testosterone in higher dose groups were similar or lower than those of negative control mice. Levels of aromatase in the ovaries of mice treated with 5 mg/d was statistically significantly lower compared to the positive control ( $p < 0.05$ ), and lower than the negative control (not statistically significant). Serum aromatase levels were statistically significantly lower in the 5 mg/d treated group compared to positive and negative controls. No significant differences were observed in higher dose groups compared to positive and negative controls.

Groups of 6 Long Evans female rats were given diets containing 0 or 1% of an inositol (isomer unspecified) for 37 d prior to mating with untreated males.<sup>86</sup> Pup growth, reproduction, and lactation parameters were evaluated. No significant difference in the rate of growth or gross appearance were observed in dams treated with an inositol versus the untreated control group. Similarly, no significant difference in the number of pups/litter was observed in control and treated groups. Lactation was inadequate in both control and treated groups; however, this effect was likely due to dietary fat insufficiencies. No other details regarding this study were provided.

### **Other**

The effect of Inositol (as *myo*-inositol) on post-implantation/post-natal development was evaluated in fertilized C57BL/6N mouse embryos in vitro (number of embryos analyzed not stated).<sup>87</sup> Naturally-fertilized, one-cell embryos were cultured with either 14  $\mu$ l/ml Inositol in cleavage medium or phosphate-buffered saline in cleavage medium. Developing embryos were scored daily for morphology and progression through cleavage stages. Embryos of the blastocyst or morula stage were analyzed for activation of the protein kinase B (PKB)/Akt pathway (known to modulate proliferation/survival cellular processes) via immunofluorescence analysis. The level of serine 473-phosphorylated Akt did not appear to be modified in embryos cultured in the presence of Inositol in the morula stage; however, it was increased at the blastocyst stage, compared to untreated controls ( $p = 0.02$ ). In 10 replicate experiments, embryos that developed to the blastocyst stage after 4 d of culture with or without Inositol were transferred to the uteri of untreated, pseudopregnant mice (number of animals used not specified). On the day of delivery, newborn animals were weighed, checked for gross abnormalities, and left to be nursed until weaning. The number of delivered animals was statistically significantly increased in embryos treated with Inositol compared to untreated controls ( $p < 0.05$ ). Somatometric development and body weights at birth, 1 wk, and 3 wk after birth were similar in control and treated embryos.

### **GENOTOXICITY STUDIES**

Details regarding the in vitro studies and the QSAR models summarized here can be found in Table 4. Inositol (as *myo*-inositol; up to 5%) was not mutagenic in in vitro assays (plate test and suspension test) performed using *Salmonella typhimurium* and *Saccharomyces cerevisiae*.<sup>88</sup> Assays were performed with and without metabolic activation. The mutagenic potential of Inositol (as *myo*-inositol) was evaluated in several QSAR models (prediction of Ames assay, chromosomal aberration assay, in vitro mouse lymphoma assay, and in vivo micronucleus assay).<sup>6</sup> The test substance was predicted to be non-genotoxic in all models.

### **CARCINOGENICITY STUDIES**

No carcinogenicity studies were found in the literature, and no unpublished data were submitted.

### **ANTI-CARCINOGENICITY STUDIES**

Inositol has been observed to have statistically significant anti-carcinogenic/tumor suppressive effects in vitro (in colorectal cell lines treated with Inositol (as *myo*-inositol) at up to 5%), in mice (orally-administered Inositol (as *myo*-inositol) at 1 - 3%; via diet or drinking water), in humans (smokers orally-administered 18 g/d Inositol (as *myo*-inositol)), and in a case report in which a patient with metastatic melanoma consumed a daily dietary supplement consisting of phytic acid and inositol (isomer unspecified; dose taken not stated).<sup>89-96</sup> Other studies performed in mice report that Inositol (as *myo*-inositol) supplementation does not have a statistically significant effect on tumor suppression (studies performed using orally-administered Inositol at 0.5 and 3%; via diet).<sup>97-99</sup>

### **OTHER RELEVANT STUDIES**

#### **Neurotoxicity**

The following study has been provided as it may provide information regarding the potential neurotoxicity of Inositol. The effect of Inositol (as *myo*-inositol) on the proliferation of cultured Schwann cells was evaluated in vitro.<sup>100</sup> Schwann

cells were isolated from the sciatic nerve of neonatal Sprague-Dawley rats and cultured with Inositol (50 – 100 µg/ml) for 24 h. Proliferation was estimated with incorporation of tritiated thymidine into DNA synthesis (experiments carried out 3 – 4 times). To determine if Inositol inhibits axolemma-stimulated proliferation of Schwann cells, axolemma was added at various concentrations to the cell culture medium. The test substance inhibited incorporation of tritiated thymidine into DNA synthesis in a dose-dependent manner (suggesting inhibitory effect on Schwann cell proliferation). In addition, Inositol also inhibited axolemma-stimulated proliferation of Schwann cells with concentrations of axolemma ranging from 1 – 16 µg protein equivalent axolemma/well.

## **DERMAL IRRITATION AND SENSITIZATION STUDIES**

### **Irritation**

#### **Animal**

The dermal irritation potential of Inositol (as *myo*-inositol; 0.1 g) was evaluated in 5 albino Hartley guinea pigs.<sup>6</sup> The test substance was moistened with physiological saline to improve contact with skin and applied to normal and abraded skin under occlusive conditions (24-h exposure). Irritation reactions were observed at 3, 24, and 48 h after patch removal. Control animals were treated according to the same protocol, with physiological saline only (number of animals used in control group not stated). No irritation was observed in any of the groups. The primary irritation index was determined to be 0.

#### **Human**

A clinical use study was performed using 40 volunteers who were instructed to apply a face cream containing 3% Inositol (as *myo*-inositol) for 5 wk.<sup>101</sup> Throughout the study, no skin irritation or allergy was reported. No other details were provided.

### **Sensitization**

A guinea pig maximization assay was performed to evaluate the sensitization potential of Inositol (as *myo*-inositol).<sup>6</sup> Test and control groups consisted of 10 and 5 female Dunkin-Hartley guinea pigs, respectively. On day 0, intradermal induction consisted of 3 injections: one consisting of an equal volume emulsion of Freund's complete adjuvant (FCA) and physiological saline, one consisting of 10% Inositol in physiological saline, and the third consisting of an equal volume of 20% Inositol in physiological saline and FCA. For dermal induction on day 7, a semi-occlusive patch containing 60% aqueous Inositol was applied for 48 h to skin that was pretreated on day 6 with sodium lauryl sulfate. Control animals were treated with water in place of Inositol. Animals were challenged on day 21 with either 30, 60, or 100% Inositol (aqueous solutions; 24-h closed patch). Skin reactions were evaluated 24 and 48 h after patch removal. The test substance was non-sensitizing.

## **OCULAR IRRITATION STUDIES**

#### **In Vitro**

A reconstructed human cornea-like epithelium test was performed using EpiOcular tissues according to Organisation for Economic Cooperation and Development (OECD) test guidelines (TG) 492.<sup>6</sup> Tissues were incubated with either the test substance (Inositol (as *myo*-inositol), 97.9% purity; 50 mg; no vehicle), the positive control (50 µl methyl acetate), or the negative control (50 µl sterile deionized water), for 6 h. All tissues were tested in duplicate. The test substance was determined to be a non-irritant (mean viability of 92.2%). Positive and negative controls gave expected results.

## **MUCOUS MEMBRANE IRRITATION STUDIES**

#### **In Vitro**

An in vitro vaginal irritation assay was performed using EpiVaginal<sup>TM</sup> tissue (reconstructed organotypic model representative of human ecto-cervical and vaginal tissue).<sup>102</sup> Inositol (isomer unspecified) was incubated with tissues at concentrations of 4, 8, and 16%, and an ET<sub>50</sub> (exposure time which reduces 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) reduction by 50%) value was determined and compared against well-defined benchmarks. ET<sub>50</sub> values for all tested concentrations were determined to be >24 h. These values are comparable to products typically applied to this region (e.g., personal lubricants) and formulated to be non-irritants. Therefore, study authors determined that Inositol is not likely to cause any mucosal irritation.

## **CLINICAL STUDIES**

### **Effects Observed with Use of Inositol for Disease/Disorder Treatment**

A review article was found in the literature summarizing available data on the use of Inositol (as *myo*-inositol) for the treatment and prevention of pathological changes associated with disease (e.g., polycystic ovary syndrome, diabetes, cancer, erectile dysfunction, psoriasis, Alzheimer's, depression, panic disorder, bulimia nervosa, obsessive-compulsive disorder) in adults.<sup>2</sup> According to the review, adverse effects related to Inositol treatment at a dose of 12 g/d or higher include nausea, flatus, loose stools, and diarrhea. The severity of these effects did not increase with higher doses (30 g/d). At a dose of 4 g/d, Inositol usage did not cause adverse effects.

In studies performed in pregnant women (4 g Inositol (as *myo*-inositol)/d throughout pregnancy), Inositol was not associated with side effects or increased risk of adverse effects of pregnancy.<sup>103</sup> However, in a meta-analysis evaluating the effect of supplementation with an inositol (isomer unspecified) on the incidence of retinopathy of prematurity, a trend towards increased mortality was observed in infants treated with the inositol versus infants in the placebo group; however, this effect was not statistically significant (it should be noted that some of these studies involved intravenous treatment (this method is not typically relevant to cosmetic exposure)).<sup>104</sup> In a limited number of psychiatric patients, mild neurological discomfort (e.g., insomnia, dizziness) was observed following treatment with Inositol (as *myo*-inositol).<sup>21</sup> Three cases of mania were reported in the literature following the use of an inositol (isomer unspecified) in patients with mental health disorders; symptoms subsided following lowering or cessation of inositol usage.<sup>105</sup> In a study in which Inositol (as *D-chiro*-inositol; 1200 mg/d) was given orally to 20 insulin-resistant women for 6 mo, serum estradiol increases and menstrual abnormalities were observed.<sup>84</sup>

### Effect of Inositol on Reproductive Dysfunction

Eighty-six idiopathic infertile couples were observed in a study evaluating the effect of a Inositol (as *myo*-inositol) vaginal suppository (dose not stated) on sperm motility, cervical mucus quality, and pregnancy rate.<sup>106</sup> In all cases of pregnancy, evaluations of gestational progress and fetal health were performed to confirm safety of treatment. Forty-three couples were treated with the Inositol vaginal suppositories, while the remaining 43 couples received placebo suppositories. Both groups underwent 1 - 3 consecutive cycles of treatment (each cycle consisted of using 3 suppositories, one every other day, during periovulatory time, prior to bedtime). Sperm analyses were performed before the first cycle of treatment, and 3 - 6 h post-coitus (following last suppository application). Treatment with Inositol improved total sperm motility ( $54.42 \pm 8.72$ ) when compared to either baseline ( $46.48 \pm 4.05$ ) and to the placebo group ( $46.21 \pm 5.33$ ). Inositol treatment resulted in mild improvement of cervical mucus quality, reducing viscosity, spinnbarkeit, and ferning. In addition, treatment with Inositol resulted in an increased pregnancy rate (18.60% pregnancy rate in Inositol-treated couples; 6.97% pregnancy rate in placebo-treated couples). Pregnancies in Inositol-treated couples were evaluated via ultrasound investigation at 12, 22, and 32 wk, and newborns were subjected to evaluation 7 - 10 d after birth. No adverse effects were observed in mothers or fetuses/newborns.

Ten male volunteers aged between 30 - 65 yr, with a BMI between 22 and 34 and moderate alteration of glycemia and/or testosterone and estradiol levels, were instructed to take Inositol (as *D-chiro*-inositol; 1 g) supplements, orally, for 1 mo.<sup>107</sup> Serum assays for evaluated parameters (testosterone, dehydroepiandrosterone sulfate, estradiol, follicle-stimulating hormone, luteinizing hormone, glycemia, insulinemia, inhibin B, and epiandrosterone) were evaluated at baseline and after treatment. Supplementation was associated with reduced levels of estrone (-85%) and estradiol (-14.4%) and increased levels of testosterone (+23.4%), dehydroepiandrosterone (+13.8%), and epiandrosterone (+39%). A non-statistically significant decrease in glycemia and insulinemia were observed following treatment. Other evaluated parameters were similar before and after treatment. No adverse effects were observed throughout treatment.

The effect of two isomers of Inositol (*myo*-inositol and *D-chiro*-inositol) on ovarian dysfunction was evaluated in female long-term lymphoma survivors (average age of 34 yr; 45 females/group) in a pilot prospective case-control study.<sup>108</sup> Treated patients were given an oral supplement of 400 mg *myo*-inositol and 45 mg *D-chiro*-inositol, 3 times per day, for 12 mo. Controls were left untreated. Levels of follicle-stimulating hormone, luteinizing hormone, progesterone, 17- $\beta$  estradiol, and anti-Müllerian hormone were evaluated at baseline and following treatment. Antral follicle counts and menstrual frequency was also evaluated. Statistically significant reductions in follicle-stimulating hormone, luteinizing hormone, and oligomenorrhea were observed in treated patients compared to baseline. Antral follicle counts of the right ovary was significantly increased in treated patients compared to baseline. When comparing untreated and treated patients, after 12 mo of treatment, a statistically significant higher mean value in follicle-stimulating hormone and luteinizing hormone and a statistically significant lower mean antral follicle count value in the right ovary were observed in untreated patients compared to treated patients. In addition, a statistically significant increase in dyspareunia and dysmenorrhea were observed in untreated patients compared to treated patients. No other evaluated parameters were significantly different between treated and untreated groups.

The effect of Inositol (as *D-chiro*-inositol) on sperm motility (evaluated as mitochondrial membrane potential (MMP)) was evaluated in patients with and without asthenozoospermia.<sup>109</sup> Semen samples from 15 patients with asthenozoospermia and 15 healthy patients were incubated with increasing concentrations of Inositol (0, 75, and 750  $\mu\text{g}/\text{ml}$ ) for 30 min. Flow cytometric analyses were performed and MMP was observed. Inositol decreased the percentage of spermatozoa with low MMP in both normozoospermic men and patients with asthenozoospermia in a concentration-dependent manner ( $p < 0.005$ ), compared to untreated control samples (suggesting improved sperm motility).

### Topical Application of *D-chiro*-Inositol in Patients with Plaque Psoriasis

A placebo-controlled, double-blind study was performed to evaluate the clinical effects of topically-applied Inositol (as *D-chiro*-inositol) on mild plaque psoriasis (46 psoriatic patients and 10 healthy subjects).<sup>32</sup> Three stable psoriatic plaques were selected for evaluation for each patient. Lesions were treated with different samples (i.e., medium without active agent, 0.25% Inositol, or 1% Inositol; 1 fingertip unit per lesion) twice a day. Test preparations also contained rapeseed, hemp, and

flaxseed oils. Patients were evaluated at baseline, after 3 wk of treatment, after 6 wk of treatment, and 2 wk after the 6-wk treatment period. No patients complained of irritation, dryness, or allergic reactions of treated regions throughout the study.

### Retrospective and Multicenter Studies

A randomized, double-masked, multi-center study was performed to evaluate the safety of treatment with an inositol (isomer unspecified) in premature infants (n = 122, 14 centers (number of infants per group not stated)).<sup>110</sup> Infants were treated with placebo (5% glucose) or with 8, 10, or 40 mg/kg/d inositol. Dosing was performed intravenously and converted to enteral when feedings were established. Once feedings were established, dosing occurred for either 10 wk chronological age, or up to 34 wk postmenstrual age, death, or discharge. Adverse events (cardiopulmonary, gastrointestinal, hematological, metabolic, renal, and respiratory effects) were monitored from 24 h prior to drug administration until 7 d after final dose administration. Adverse events and co-morbidities were fewer in the inositol-treated group compared to the placebo-treated group (but not in a statistically significant manner).

### SUMMARY

The safety of Inositol as used in cosmetics is reviewed in this safety assessment. Inositol is reported to function in cosmetics as a hair-conditioning agent and humectant. According to 2023 VCRP data, Inositol is used in 212 total formulations (185 leave-on formulations and 27 rinse-off formulations). RLD collected in 2024 indicate that Inositol is used in 1167 total formulations. This ingredient is reported to be used at up to 4% in face and neck products.

More than 98% of total ingested Inositol (as *D-chiro*-inositol) was absorbed from the gastrointestinal tract in an assay in which animals were given a diet containing 0.23% Inositol for at least 1 mo plus 1 wk. The mean serum concentrations of 3 groups of rats given 2 g/kg Inositol (as *myo*-inositol) in distilled water were 54.4, 43.9, and 44.6 µg/ml. Supplementation of the diet of pregnant rats with 0.5% Inositol (as *myo*-inositol) resulted in increased levels of Inositol in the plasma, liver, kidneys, and intestines of offspring, and increased levels of Inositol in the milk and mammary tissues of dams. A maximum plasma concentration of 0.23 mM was observed in 8-d-old rats given a formula supplemented with 114 mg/100 ml Inositol (as *myo*-inositol). In a study performed in 5 female subjects given 100 mg/kg bw Inositol (as *myo*-inositol) in water (oral ingestion), the highest urinary Inositol concentration was approximately 550 µmol/mmol creatinine 275 min after test substance administration. Mean  $C_{max}$  values in subjects administered a soft gel containing 600 g Inositol, 2000 mg of Inositol powder, a soft gel containing 1200 mg Inositol, and 4000 mg of Inositol powder were 31.5, 36.3, 41.5 and 45 µmol/l, respectively (soft gels and powders contained the isomer *myo*-inositol).

An acute oral LD<sub>50</sub> of 10 g/kg bw was established for Inositol (as *myo*-inositol) in an acute oral toxicity assay performed in mice. QSAR analysis of Inositol (as *myo*-inositol) resulted in a predicted acute oral LD<sub>50</sub> of 19.5 g/kg *myo*-inositol (in rats).

No significant differences in weight gain and patterns of lipids in the liver were observed in male Wistar rats of different ages (20-d-old and 3-mo-old) given Inositol (as *myo*-inositol; up to 1000 mg/kg bw/d in 20-d-old rats and up to 5000 mg/kg bw/d in 3-mo-old rats) via gavage for 45 d, compared to controls. No adverse effects relating to hormone levels, BMI, insulinemia, and insulin resistance were observed in 10 healthy women given 1200 mg Inositol (as *D-chiro*-inositol) once daily for 1 mo; however, increased testosterone and asprosin levels were observed. No alerts for short-term oral toxicity or organ toxicity were raised for Inositol (as *myo*-inositol) using QSAR analysis.

Altered ovarian histology, and a statistically significant increase in serum testosterone and statistically significant decrease in aromatase were apparent in mice given Inositol (as *D-chiro*-inositol) in amounts of 5 mg/d in drinking water for 21 d. No test substance-related adverse developmental or reproductive effects were observed in offspring in an assay in which female rats were treated with 1% of an inositol (isomer unspecified; via diet) for 37 d prior to mating with untreated males. An increase in the number of delivered animals (compared to controls) and normal somatometric development was observed in mouse pups that were cultured with 14 µl/ml Inositol (as *myo*-inositol) in the embryo stage prior to the implantation into the uteri of pseudopregnant untreated mice.

Inositol (as *myo*-inositol; up to 5%) was not mutagenic in in vitro assays (plate test and suspension test; with and without metabolic activation) performed using *S. typhimurium* and *S. cerevisiae*. The mutagenic potential of Inositol (as *myo*-inositol) was evaluated in several QSAR models (prediction of Ames assay, chromosomal aberration assay, in vitro mouse lymphoma assay, and in vivo micronucleus assay). The test substance was predicted to be non-genotoxic in all models.

Inositol (as *myo*-inositol) has been observed to have statistically significant, anti-carcinogenic/tumor suppressive effects in vitro and in vivo. Conversely, some studies performed in mice report that Inositol (as *myo*-inositol) supplementation does not have a statistically significant effect on tumor suppression.

Inositol (as *myo*-inositol; 50 – 100 µg/ml) resulted in a dose-dependent inhibited proliferation of Schwann cells in an in vitro assay. The test substance also inhibited axolemma-stimulated proliferation of Schwann cells.

No irritation was observed in a dermal irritation assay in which moistened Inositol (as *myo*-inositol; 0.1 g) was applied to the normal and abraded skin of 5 guinea pigs under occlusive conditions (24-h exposure). No skin irritation or allergy was reported in a clinical use study in which 40 volunteers applied a face cream containing 3% Inositol (as *myo*-inositol) for 5

wk. Inositol (as *myo*-inositol) was determined to be non-sensitizing in a guinea pig maximization assay (intradermal injection induction: 10 - 20% Inositol; epicutaneous induction: 60% Inositol (48-h closed patch); challenge: 30 - 100% Inositol (24-h closed patch).

Inositol (as *myo*-inositol) was considered to be a non-irritant in an EpiOcular assay in which tissues were incubated with 50 mg Inositol for 6 h. The mean tissue viability was reported to be 92.2%.

Study authors determined that Inositol (as *myo*-inositol; up to 16%) was not likely to cause any mucosal irritation in an EpiVaginal™ assay. ET<sub>50</sub> values for all tested concentrations were determined to be >24 h, and were comparable to products typically applied to the vaginal region and formulated to be non-irritants.

Inositol has been studied for the treatment of various illnesses. Adverse effects reported following use as an oral supplement include gastrointestinal issues (at doses of 12 g/d or higher), mild neurological discomfort, menstrual abnormalities, and mania in case reports in several individuals with mental health disorders. A trend towards increased mortality was observed in a meta-analysis evaluating the effect of inositol (isomer unspecified) supplementation in preterm infants; however, this effect was not statistically significant (some studies in this analysis were intravenous).

An increased pregnancy rate (18.60%) compared to placebo-treated controls (6.97%) was observed in study in which 86 couples were given an Inositol (as *myo*-inositol) vaginal suppository or a placebo suppository to evaluate the effect of Inositol on fertility parameters. Reduced levels of estrone, estradiol, and increased levels of testosterone, dehydroepiandrosterone, and epiandrosterone were observed in an assay in which 10 male volunteers were given Inositol (as *D-chiro*-inositol) as an oral supplement for 1 mo. The effect of an oral supplement containing 400 mg *myo*-inositol and 45 mg *D-chiro*-inositol (taken 3x/d for 12 mo) on ovarian dysfunction was evaluated in long-term female lymphoma survivors. When comparing untreated and treated patients, after 12 mo of treatment, a statistically significant higher mean value in follicle-stimulating hormone and luteinizing hormone, and a statistically significant lower mean antral follicle count value in the right ovary were observed in untreated patients compared to treated patients. Improved MMP was observed in the sperm samples of normozoospermic men and patients with asthenozoospermia when sperm was incubated with Inositol (as *D-chiro*-inositol for 30 min).

The effect of topically applied Inositol (as *D-chiro*-inositol (0.25 or 1%)) on psoriasis plaques was evaluated in 46 psoriatic patients and 10 healthy volunteers. No patients complained of irritation, dryness, or allergic reactions of treated regions throughout the study.

A multi-center study was performed to evaluate the safety of treatment with an inositol (up to 40 mg/kg/d; intravenous treatment converted to enteral when feedings established; isomer unspecified) in 122 premature infants. Adverse events and co-morbidities were fewer in the inositol-treated group compared to the placebo-treated group (but not statistically significantly so).

## DISCUSSION

The Panel reviewed the available, relevant data on Inositol and concluded that this ingredient is safe in cosmetics in the present practices of use and concentration described in this safety assessment. Although Inositol has 9 potential geometric isomers, according to the *Dictionary*, the 2 isomers used in the production of Inositol include *myo*-inositol and *D-chiro*-inositol.

The safety of this ingredient is supported by its widespread use, GRAS status, endogenous nature, low concentrations of use, and robust safety data profile, which reports no evidence of irritation or sensitization and a lack of positive alerts in various toxicological studies. The Panel did note reproductive effects in an oral study performed in mice; however, the Panel determined that the effects observed in this study were irrelevant to cosmetic use as the doses in this assay were much higher than what would result via cosmetic exposure.

In addition, the Panel noted that microbial fermentation may be used in the production of this ingredient. They stressed that the cosmetics industry should continue to minimize impurities (including microbial contaminants) in cosmetic formulations according to limits set by the US FDA and Environmental Protection Agency (EPA).

The Panel also discussed the issue of incidental inhalation exposure resulting from this ingredient; for example, Inositol is reported to be used in a face powder (concentration not provided) and could be possibly inhaled. Inhalation toxicity data were not available. Coupled with the small actual exposure in the breathing zone and the low concentrations at which this ingredient is used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <https://www.cir-safety.org/cir-findings>.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

**CONCLUSION**

The Expert Panel for Cosmetic Ingredient Safety concluded that Inositol 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
<b>myo-Inositol</b>		
Physical Form	solid	6
Odor	odorless	10
Color	white	6
Molecular Weight (g/mol)	180.16	9
Density (g/cm <sup>3</sup> @ 20°C)	1.752	6
Vapor Pressure (mm Hg)	≥ 7.606 - ≤ 20.079	6
Melting Point (°C)	225 - 227	6
Boiling Point (°C)	384.72	6
Water Solubility (g/100 g water @ 60°C)	28	6
log K <sub>ow</sub>	-2.08	6
<b>D-chiro-Inositol</b>		
Physical Form	solid	11
Color	white to off-white	11
Molecular Weight (g/mol)	180.16	8
Density	1.28 (estimated)	11
Melting Point (°C)	230	11
Boiling Point (°C)	232.96 (estimated)	11
Water Solubility (g/L @ 11°C)	403.4	11
log K <sub>ow</sub>	-2.60	11

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

	# of Uses		Max Conc of Use
	RLD (2024) <sup>25</sup>	VCRP (2023) <sup>24</sup>	% (2022) <sup>26,27</sup>
<b>Totals*</b>	<b>1167</b>	<b>212</b>	<b>0.000025 - 4</b>
<b>summarized by likely duration and exposure**</b>			
<b>Duration of Use</b>			
Leave-On	***	185	0.001 - 4
Rinse-Off	***	27	0.00025 - 1
Diluted for (Bath) Use	***	NR	NR
<b>Exposure Type**</b>			
Eye Area	***	20	1
Incidental Ingestion	***	1	NR
Incidental Inhalation-Spray	***	91 <sup>a</sup> ; 54 <sup>b</sup>	NR
Incidental Inhalation-Powder	***	1; 54 <sup>b</sup>	0.001 - 4 <sup>c</sup>
Dermal Contact	***	194	0.00067 - 4
Deodorant (underarm)	***	NR	NR
Hair - Non-Coloring	***	17	0.000025
Hair-Coloring	***	NR	NR
Nail	***	NR	NR
Mucous Membrane	***	4	0.00067
Baby Products	***	NR	NR
<b>as reported by product category</b>			
<b>Baby Products</b>			
Other Baby Products	1 (l.o.)	NR	NR
<b>Eye Makeup Preparations (other than children's eye makeup preparations)</b>			
Eyeliners	1	NR	NR
Eye Shadow	NR	7	NR
Eye Lotion	11	8	1
Eye Makeup Removers	2	NR	NR
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	7	NA	NA
Other Eye Makeup Preparations	3	5	NR
<b>Hair Preparations (non-coloring)</b>			
Hair Conditioner	28 (l.o.); 33 (r.o.)	5	0.000025
Rinses (non-coloring)	20	NR	NR
Shampoos (non-coloring)	1 (l.o.); 54 (r.o.)	5	NR
Tonics, Dressings, and Other Hair Grooming Aids	48	2	NR
Other Hair Preparations	55 (l.o.); 25 (r.o.)	5	NR
<b>Hair Coloring Preparations</b>			
Hair Dyes and Colors (all types requiring caution statements and patch tests)	255	NR	NR
Hair Tints	15	NR	NR
Hair Rinses (coloring)	2 (r.o.)	NR	NR
Hair Shampoos (coloring)	3 (r.o.)	NR	NR

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

	# of Uses		Max Conc of Use
Other Hair Coloring Preparations	3 (l.o.); 4 (r.o.)	NR	NR
<b>Makeup Preparations (not eye; not children's)</b>	<b>55</b>		
Blushers and Rouges	4	NR	NR
Face Powders	17	1	NR
Foundations	28 (traditional application)	2	NR
Lipstick and Lip Glosses	7	1	NR
Makeup Bases	9 (traditional application)	2	0.001
Other Makeup Preparations	4 (l.o.)	NR	NR
<b>Oral Products</b>	<b>1</b>		
Other Oral Products	1	NR	NR
<b>Personal Cleanliness</b>	<b>24</b>		
Bath Soaps and Body Washes	20	3	0.00067
Disposable Wipes	1	NA	NR
Other Personal Cleanliness Products	2 (l.o.); 2 (r.o.)	NR	NR
<b>Shaving Preparations</b>	<b>5</b>		
Aftershave Lotions	2	NR	NR
Beard Softeners	2	NR	NR
Pre-shave Lotions (all types)	1	NR	NR
Shaving Creams (aerosol, brushless, and lather)	NR	3	NR
<b>Skin Care Preparations (creams, lotions, powder, and sprays)</b>	<b>601</b>		
Cleansing (cold creams, cleansing lotions, liquids, and pads)	43	9	0.001 – 0.0025
Depilatories	1	NR	NR
Face and Neck (excluding shaving preparations)	370 (l.o.); 35 (r.o.)	44	0.001 – 4
Body and Hand (excluding shaving preparations)	36 (l.o.); 8 (r.o.)	10	0.001 – 0.3
Foot Powders and Sprays	1	NR	NR
Moisturizing	172	76	0.001 – 2
Night	10	8	NR
Paste Masks (mud packs)	24	2	1
Skin Fresheners	10	4	NR
Other Skin Care Preparations	58 (l.o.); 10 (r.o.)	9	NR
<b>Suntan Preparations</b>	<b>8</b>		
Suntan Gels, Creams, and Liquids	6	NR	NR
Indoor Tanning Preparations	1 (traditional application)	NR	NR
Other Suntan Preparations	2	1	NR
<b>Other Preparations (i.e., those preparations that do not fit another category)</b>	<b>35</b>	NA	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>)

\*\*\*Because RLD are product-centric and not ingredient-centric, 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.

<sup>a</sup> It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

<sup>b</sup> 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.

<sup>c</sup> It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 3. Oral ADME studies

Parameter Measured	Inositol Isomer	Animals	No./Group	Vehicle/Dose	Dose/Protocol	Results	References
<b>ANIMAL</b>							
Absorption and Excretion	<i>D-chiro</i> -inositol	Male Sprague-Dawley rats	3	diet containing 0.23% <i>D-chiro</i> -inositol	Animals fed diet containing a mean amount of 12.94 nmol/mg Inositol for at least 1 mo, then housed in metabolic cages and fed diet for 1 wk; urine and feces collected for 24 h (study does not state when 24 h collection period occurred). The mean intake of <i>D-chiro</i> -inositol was 921 $\mu$ mol/kg bw/d.	More than 98% of the total ingested Inositol was absorbed from the gastrointestinal tract. The mean total amount of <i>D-chiro</i> -inositol found in the stool and urine was 6.2 and 42.3 $\mu$ mol/kg bw/d, respectively; these minimal amounts suggest that the bulk of the ingested <i>D-chiro</i> -inositol was metabolized.	79
Metabolism	<i>myo</i> -inositol	Male Wistar rats	3/group	2000 mg/kg in distilled water	Animals treated via gavage; blood samples taken at different time intervals up to 48 h post-administration as follows:  Group 1: 0, 0.25, 0.5, 1, 24 h Group 2: 0, 2, 4, 8, 12, 24 h Group 3: 0, 1.5, 36, 48 h	The highest mean Inositol concentration in serum samples was observed within the first hour after administration in all test animals of group 1. Concentration of the test substance in samples decreased after the maxima peak; however, after 24 h, levels were still higher than baseline. The biological half-life was determined to be 4.08 h. Within 24 hours, the average <i>myo</i> -inositol concentrations in the serum of Group 1 and Group 2 rats were 54.4 $\mu$ g/ml and 43.9 $\mu$ g/ml, respectively. For Group 3 rats, the average concentration was 44.6 $\mu$ g/ml within 48 hours.	20
Distribution	<i>myo</i> -inositol	Pregnant female Holtzman rats	35/group	0.5% in diet	On 7 <sup>th</sup> day of gestation, animals were divided into 2 groups and given either a purified diet with or without 0.5% Inositol for 120 d (during gestation and lactation); pups were fed corresponding diet after weaning until 3 mo of age; free <i>myo</i> -inositol content of tissues, amniotic fluid, milk, and plasma was measured via gas-liquid chromatography; lipid-bound Inositol in the form of phosphatidylinositol was quantified via a lipid extract of tissue	Supplementation of the diet with Inositol significantly increased the levels of Inositol in plasma, liver, kidney, and intestine of pups at all ages examined, and significantly increased the levels of Inositol in the milk and mammary tissue during lactation.	80
Distribution	<i>myo</i> -inositol	Neonatal Holtzman rats	4/sex/group	gastric intubation: 114 mg/100 ml formula (supplemented formula)  7.44 mg/100 ml formula (restricted formula)  supplemented diet: 250 mg/100 g diet  (Inositol content of Inositol-restricted diet not stated)	6-d-old rat pups fed liquid formula via stomach tube using either a Inositol-restricted formula, or a Inositol supplemented formula (pups fed 0.3 ml formula/g bw every 4 h); at 16 d of age, pups fed Inositol restricted formula were fed purified diet deficient in <i>myo</i> -inositol, and pups fed Inositol supplemented formula were fed an identical diet supplemented with Inositol until 72 d of age; tissues obtained and observed at selected ages (from 6- to 72-d-old) of each dietary group; blood removed via cardiac puncture	Plasma Inositol levels of animals fed the Inositol restricted formula and diet were significantly lower ( $p < 0.05$ ) than those of Inositol supplemented rats at all ages except at day 72. The maximum plasma concentration of Inositol was approximately 0.23 mM (in 8-d-old Inositol supplemented rat). Most tissues (testes, kidneys, liver) examined from rats fed the Inositol-deprived formula and diet had lower free Inositol levels compared to tissues of the Inositol supplemented group, excluding the cerebrum and cerebellum. Differences between Inositol levels in testis, lens, and kidney were significant ( $p < 0.05$ ) for 6 versus 18 d of age within each dietary group (increased amounts in older rats).	81

Table 3. Oral ADME studies

Parameter Measured	Inositol Isomer	Animals	No./Group	Vehicle/Dose	Dose/Protocol	Results	References
<b>HUMAN</b>							
Distribution and Excretion	<i>myo</i> -inositol	Human subjects	5 females	100 mg/kg bw; aqueous solution	Baseline measurements of Inositol via blood sample taken prior to treatment; subjects ingested test substance and blood was drawn 20, 40, 60, 90, 180, and 270 min after ingestion; urine samples taken 0, 180, and 270 min after ingestion	After ingestion, the <b>observed</b> mean serum concentration of <i>myo</i> -inositol increased from 19.9 µmol/l to an observed maximum of 96.5 µmol/l after 90 min; the <b>estimated</b> mean serum <i>myo</i> -inositol increased significantly from 20.8 µmol/l to an estimated maximum of 101.5 µmol/l after 180 min (this indicates that the <b>actual</b> maximum <i>myo</i> -inositol serum concentration is located between 90 – 180 min post-ingestion.  The observed and estimated concentrations decreased to 77.3 µmol/l and 72.5 µmol/l after 270 min, respectively.  The highest urinary <i>myo</i> -inositol concentration was approximately 550 µmol/mmol creatinine 275 min after administration	82
Absorption	<i>myo</i> -inositol	Human subjects	20 total (8 males and 12 females)	Phase 1: soft gel capsule containing 600 mg Inositol  Phase 2: 2000 mg Inositol powder  Phase 3: soft gel capsule containing 1200 mg Inositol  Phase 4: 4000 mg Inositol powder	Patients were treated with each of the test substances orally, in phases. Each phase was separated by a washout period of 15 d. Pharmacokinetic parameters were evaluated based on the analysis of Inositol plasma concentrations. Blood samples collected at baseline, 30, 60, 90, 120, 180, 300, 420, 540, and 1440 min post-administration.	Mean C <sub>max</sub> : -soft gel containing 600 mg Inositol: 31.5 µmol/l at 180 min -2000 mg Inositol powder: 36.3 µmol/l at 180 min -soft gel containing 1200 g Inositol: 41.5 µmol/l at 120 min -4000 mg Inositol powder: 45 µmol/l at 122 min	83

C<sub>max</sub> = maximum observed plasma concentration; T<sub>max</sub> = time to peak concentration

**Table 4. Genotoxicity studies**

Inositol Isomer	Vehicle	Concentration	Test System	Procedure	Results	Reference
<b>In Vitro</b>						
<i>myo</i> -inositol	saline and DMSO	up to 5%	<i>S. typhimurium</i> strains TA 1535, TA 1537, and TA 1538	<p>Plate test with and without metabolic activation:</p> <p>-For non-activated procedure: cells of a log phase culture of the bacterial indicator strains spread over surface of a plate, and measured amount of test chemical added to cells; 4 d incubation</p> <p>-For activated procedure: test chemical added to cells, aliquot of mixture spread on test plate; reaction mixture plus tissue extract spotted on surface of plate; 4 d incubation</p> <p>-Negative controls: saline and DMSO</p> <p>-Positive controls: ethyl methanesulfonate, quinacrine mustard, nitrosofluorene, dimethylnitrosamine, and 2-acetylaminofluorene</p>	Non-mutagenic	88
<i>myo</i> -inositol	saline and DMSO	up to 5%	<i>S. typhimurium</i> strains TA 1535, TA 1537, and TA 1538; and <i>S. cerevisiae</i> strain D4	<p>Suspension test with and without metabolic activation; bacteria and yeast cultures suspended in saline; cells plus test chemical added to flask; 4 h treatment for yeast test and 1 h treatment for bacteria test; flasks shaken during treatment and set in ice after treatment; aliquots of cells removed; samples placed on selected media; bacterial plates scored after incubation for 48 h and yeast plates scored after 3-5 d of incubation; negative controls: saline and DMSO; positive controls: ethyl methanesulfonate, quinacrine mustard, nitrosofluorene, dimethylnitrosamine, and 2-acetylaminofluorene</p>	Non-mutagenic	88
<b>Computational</b>						
<i>myo</i> -inositol	-	-	<i>S. typhimurium</i> strains TA 102, TA 100, TA 98, TA 1537, TA 1535	QSAR – Ames assay prediction; with and without metabolic activation; Times v.2.27.19.13 in QSAR Toolbox	No mutagenic potential predicted	6
<i>myo</i> -inositol	-	-	Chinese hamster ovary and lung cells	QSAR – in vitro cytogenicity/chromosome aberration assay prediction; with and without metabolic activation; Times v.2.27.19.13 in QSAR Toolbox	No mutagenic potential predicted	6
<i>myo</i> -inositol	-	-	NR	QSAR – in vitro mouse lymphoma assay prediction; with and without metabolic activation; OASIS TIMES v.2.31.2.82	No mutagenic potential predicted	6
<i>myo</i> -inositol	-	-	Mammalian erythrocytes and peripheral blood	QSAR – in vivo micronucleus assay prediction; Times v.2.27.19.13 in QSAR Toolbox	No mutagenic potential predicted	6

DMSO – dimethyl sulfoxide; NR = not reported; QSAR = quantitative structure activity relationship

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**Concentration of Use by FDA Product Category – Inositol**

<b>Product Category</b>	<b>Maximum Concentration of Use</b>
Eye lotions	1%
Hair conditioners	0.000025%
Makeup bases	0.001%
Bath soaps and detergents	0.00067%
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	0.001-0.0025%
Face and neck products Not spray	0.001-4%
Body and hand products Not spray	0.001-0.3%
Moisturizing products Not spray	0.001-2%
Paste masks and mud packs	1%

Information collected in 2022

Table prepared: July 6, 2022

Updated October 15, 2024: Maximum concentration for face and neck products increased from 2% to 4%