Amended Safety Assessment of Propylene Carbonate as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: May 16, 2025
Panel Meeting Date: June 9 – 10, 2025

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. 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 Ferguson, M.S., Senior Scientific Analyst/Writer, CIR.

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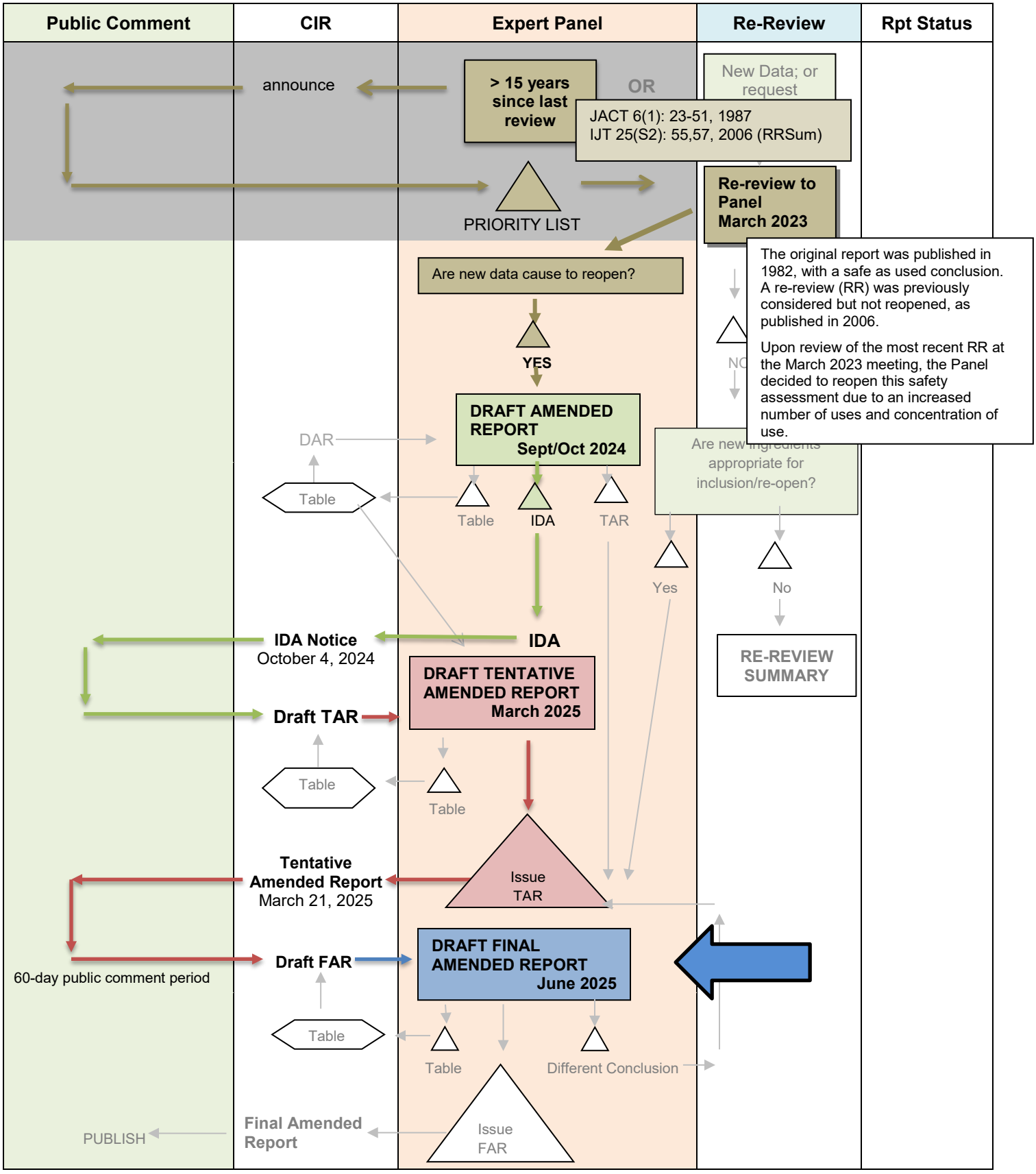
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Propylene Carbonate

MEETING June 2025



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Ferguson, M.S., Senior Scientific Analyst/Writer, CIR
Date: May 16, 2025
Subject: Amended Safety Assessment of Propylene Carbonate as Used in Cosmetics

Enclosed is the Draft Final Amended Report on the Safety of Propylene Carbonate as Used in Cosmetics. (It is identified as *report_PropyleneCarbonate_062025* in the pdf document). At the March 2025 meeting, the Panel issued a Tentative Amended Report for public comment with the conclusion that Propylene Carbonate is safe in cosmetics in the present practices of use and cosmetics as described in the safety assessment, when formulated to be non-irritating.

Since that meeting, no new data have been received. Comments on the Tentative Amended Report that were received have been addressed (*PCPCcomments_PropyleneCarbonate_062025*; *response-PCPCcomments_PropyleneCarbonate_062025*).

According to 2023 VCRP survey data, Propylene Carbonate is reported to be used in 882 total formulations. The results of the concentration of use survey conducted by the Council in 2022 indicate that this ingredient is used at up to 17.9% in leave-on formulations. In 2002/2003, this ingredient was reported to be used in 178 formulations, at up to 5%.

Additional supporting documents for this report package include a flow chart (*flow_PropyleneCarbonate_062025*), the original report published in 1987 (*originalreport1987_PropyleneCarbonate_062025*), the re-review published in 2006 (*rereview2006_PropyleneCarbonate_062025*), a report history (*history_PropyleneCarbonate_062025*), a search strategy (*search_PropyleneCarbonate_062025*), a data profile (*dataprofile_PropyleneCarbonate_062025*), minutes from meetings at which the original report and re-review were discussed (*originalminutes_PropyleneCarbonate_062025*) and transcripts from all the recent meetings at which Propylene Carbonate was discussed (*transcripts_PropyleneCarbonate_062025*).

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

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 14, 2025

SUBJECT: Tentative Amended Report: Amended Safety Assessment of Propylene Carbonate as Used in Cosmetics (release date: March 21, 2025)

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

Method of Manufacture – This section states: "Propylene Carbonate is manufactured by reacting propylene oxide and carbon dioxide….", "Propylene Carbonate was reported, by one cosmetic manufacturer, to be synthesized from propylene oxide and carbon dioxide…" and "typically synthesized through carboxylation of propylene oxide". These statements all seem to be describing the same method. Since a "cosmetic manufacturer" (please revise to "cosmetic ingredient manufacturer) reported the method, the statement "it is unknown whether these methods are used in the manufacturing of cosmetic ingredients" should not apply to this method.

Cosmetic Use; Discussion – Table 2 indicates that 111 airbrush foundations were reported to the FDA RLD. Therefore, the following should be revised. "Some products containing Propylene Carbonate may be marketed for use with airbrush delivery systems." ("may be" should be replaced with "are")

Dermal Penetration – Please correct "detector fluid" to "receptor fluid"

Acute, Inhalation, old report summary – The subcutaneous exposure study should be removed from the Inhalation section.

Repeated-Dose – It should be made clear that the "toxic effects" observed in the 9-day inhalation study were signs of irritation. In the text, it would be helpful to note that the 90-day study was an OECD TG 413 study and that the only effects observed were the described ocular effects and that this was also observed in some controls.

Summary – It would be helpful to note both doses (16 or 29.1 ml/kg) used in the oral LD_{50} study. Please indicate that the toxic effects in the 9-day inhalation study were signs of irritation.

Discussion – Please state that the photosensitization study was on a formulation containing 20% Propylene Carbonate. It would be helpful to state that the animals were exposure 5 days/week, 6 hours/day in the 90-day inhalation study.

Table 3 – In the oral 90-day study, it would be helpful to know if body weights were 10% or more below the controls.

In the Results column of the 90-day inhalation study, it would be helpful to note that the periocular swelling was the only treatment-related effect observed in this OECD guideline study.

Table 5 – Please add "%" to the EC_{90} value of 17.

Propylene Carbonate - June 2025 – Priya Ferguson, Writer	
Comment Submitter: Personal Care Products Council **Date of Submission: April 14, 2025**	
Comment	**Response/Action**
Method of Manufacture – This section states: "Propylene Carbonate is manufactured by reacting propylene oxide and carbon dioxide….", "Propylene Carbonate was reported, by one cosmetic manufacturer, to be synthesized from propylene oxide and carbon dioxide…" and "typically synthesized through carboxylation of propylene oxide". These statements all seem to be describing the same method. Since a "cosmetic manufacturer" (please revise to "cosmetic ingredient manufacturer) reported the method, the statement "it is unknown whether these methods are used in the manufacturing of cosmetic ingredients" should not apply to this method.	The "it is unknown whether these methods are used in the manufacturing of cosmetic ingredients" refers to the methods listed after the statement, in unitalicized text (these methods were not reported by a cosmetic manufacturer).
Cosmetic Use; Discussion – Table 2 indicates that 111 airbrush foundations were reported to the FDA RLD. Therefore, the following should be revised. "Some products containing Propylene Carbonate may be marketed for use with airbrush delivery systems." ("may be" should be replaced with "are")	Addressed
Dermal Penetration – Please correct "detector fluid" to "receptor fluid"	Addressed
Acute, Inhalation, old report summary – The subcutaneous exposure study should be removed from the Inhalation section.	Addressed
Repeated-Dose – It should be made clear that the "toxic effects" observed in the 9-day inhalation study were signs of irritation. In the text, it would be helpful to note that the 90-day study was an OECD TG 413 study and that the only effects observed were the described ocular effects and that this was also observed in some controls.	Details such as test guidelines are not typically included in text but can be found in tables.
Summary – It would be helpful to note both doses (16 or 29.1 ml/kg) used in the oral LD50 study. Please indicate that the toxic effects in the 9-day inhalation study were signs of irritation.	Addressed
Discussion – Please state that the photosensitization study was on a formulation containing 20% Propylene Carbonate. It would be helpful to state that the animals were exposure 5 days/week, 6 hours/day in the 90-day inhalation study.	The discussion currently states that the photosensitization assay was performed using 20% Propylene Carbonate
Table 3 – In the oral 90-day study, it would be helpful to know if body weights were 10% or more below the controls.,	Study did not specify.
In the Results column of the 90-day inhalation study, it would be helpful to note that the periocular swelling was the only treatment-related effect observed in this OECD guideline study.	Addressed
Table 5 – Please add "%" to the EC90 value of 17.	Addressed

Propylene Carbonate – History

October 1994

- Panel reviews Draft Report and issues an IDA due to lack of mutagenicity studies

November 1985

- Panel reviews Draft Tentative Report and issues a Final Report with conclusion that Propylene Carbonate is safe as used

September 2004

- Panel re-reviews Propylene Carbonate and determines that the report should not be re-opened

March 2023

- Panel re-reviews Propylene Carbonate and determines to re-open due to increased concentration and frequency of use
- Patch test received on serum containing 17.84% (PCPC submission)
- 5-d facial use test received on serum containing 17.84% (PCPC submission)
- Clinical use test received on serum containing 17.84% (PCPC submission)

May 2023

- HRIPT received on product containing 17.84% (PCPC submission)

September 2024

- Panel reviews Draft Amended Report; issued IDA
- Comments received on Draft Amended Report from Personal Care Products Council

March 2025

- Panel reviewed Tentative Amended Report
- Panel issued TAR for public comment

April 2025

- Comments received on Tentative Amended Report from PCPC

June 2025

- Panel reviewed FAR

Propylene Carbonate Data Profile* – June 2025 – Writer, Priya Ferguson																														
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Propylene Carbonate	**XO**	**XO**	O	X	XO	X	X O	X O	X	O	X	X		X	XO	X	X			XO	XO			XO	O	X	XO		

* "X" indicates that new data were available in a category for the ingredient
* "O" indicates that old data were available in a category for the ingredient

Propylene Carbonate

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Propylene Carbonate	108-32-7	x	x						x	x							x

Search Strategy

- "Propylene Carbonate" and "108-32-7" searched on links listed below

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 databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx

- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

MARCH 2023 MEETING – CONSIDERATION TO RE-OPEN/SECOND RE-REVIEW

Belsito Team – March 6, 2023

DR. BELSITO: Propylene carbonate. So this is a rereview, and the Expert Panel first published our safety of this in '87. Conclusion, safe as a cosmetic ingredient, present practice of use and concentration. We looked at a rereview in 2006 and reaffirmed that. It's been 15 years, so we're looking at it again. There's been a marked increase in the concentration of use. And I thought we needed to reopen it because right now it would be insufficient for sensitization at the current use concentration. We don't have a UV absorption spectrum.

I don't know if we need it. We'd have to say formulate to be nonirritating. We need the respiratory boilerplate, unless sub-chronic inhalation covers that, and we need to exclude the airbrush uses. So lots of reasons to reopen this report.

DR. SNYDER: Agreed.

DR. KLAASSEN: Agreed.

DR. BELSITO: Allan?

DR. RETTIE: Okay, go ahead.

DR. BELSITO: Okay. We're reopening it.

DR. RETTIE: Can you hear me now? I was kicked out for a while. I think I'm back on, though.

DR. BELSITO: Yeah. We can hear you, Allan.

DR. RETTIE: Yeah, I agree.

DR. BELSITO: Okay, so we're going to reopen it, Priya.

MS. CHERIAN: Okay.

Cohen Team – March 6, 2023

DR. COHEN: We'll move on to propylene carbonate. Okay, get rid of that. Okay, so propylene carbonate was first published in a review in 1987, with the conclusion of safe. And the 1987 conclusion was reaffirmed in 2006. We've got some new toxicologic data. We know that propylene carbonate is used at up to 5 percent as an inactive ingredient in a FDA-approved topical drug formulation. We have frequency of use that has increased quite a bit from 178 uses, in 2002, to 911 uses in 2022.

And in 2003 its use was up to five percent. And according to 2022 concentration of use, propylene carbonates used up to 17.9 percent. It's used in baby products as well. And from the old report, the max use is close to sensitization studies which have appeared to have some positives, at least that's what I could see in the old report, but any comments, thoughts?

DR. TILTON: So, I was recommending to reopen primarily based on the new ocular irritation data and increased use in eye makeup preparations.

DR. ROSS: I would second that. I mean, I think also the increased uses, increase concentration, the new data with ocular, yeah, reopen.

DR. COHEN: Tom?

DR. SLAGA: I agree.

DR. COHEN: Yeah. I had it as a reopen as well. All right, any --

DR. ROSS: We had a propylene glycol in there as well, we had probably caught that.

DR. COHEN: What do you mean?

DR. ROSS: It was just a typo. Propylene Glycol -- was misidentified as propylene glycol on page four. I'm sure it's --

DR. COHEN: Okay. And we're sure that it was meant to be propylene carbonate and not glycol?

DR. ROSS: Yeah.

DR. COHEN: Okay. Any other comments on propylene carbonate? It's used as an excipient in tacrolimus ointment.

Full Panel – March 7, 2023

DR. BERGFELD: Okay. Moving on to the next ingredient in this other items category. Propylene carbonate. Dr. Belsito.

DR. BELSITO: Yeah, so the panel reviewed the safety of this in '87 with a conclusion that propylene carbonate is safe as a cosmetic ingredient in present practice of use and concentration as stated in the report. We looked at it in re-review in 2006, and reaffirmed the 1987 conclusion. But it's been more than 15 years, so we're looking at it again.

And since we last looked at it, there's been a marked increase in the concentration of use of this material. And we felt that the data that we currently have is insufficient to support its safety. We need sensitization and concentration of use. We need some UV absorption, possibly. It appears that it might be irritating, so we want to reopen this report.

DR. BERGFELD: That's a motion?

DR. COHEN: Second.

DR. BERGFELD: Okay. Any other discussion? There have been some items that have been requested as a need. Anything else to say about this ingredient other than reopen it?

DR. COHEN: We harmonize exactly the way Don reported.

DR. BERGFELD: Okay. I'm going to call the question then. All those opposing? Abstaining? This ingredient is reopened.

SEPTEMBER 2024 MEETING – INITIAL REVIEW/DRAFT AMENDED REPORT

Belsito Team – September 30, 2024

DR. RETTIE: Oh, it's a massive document.

DR. BELSITO: Okay, propylene carbonate. In '87, we published a safety assessment with a conclusion that it's safe as a cosmetic ingredient, present practice of use and concentration. We did a re-review in 2004, reaffirmed the '87 conclusion. That was published in 2006. And again, more than 15 years, so we're looking at it again. 2023, we determined to reopen it due to increased frequency and concentration of use. VCRP data, it's reported to be used in 882 total formulations. With the Cosmetic Direct data, it's up 13,551 total formulations. And again, my pages are all screwed up. Yeah. Results of concentration of use in 2022 indicate it's used up to 17.9 percent. Am I on the right document now?

MS. FIUME: Yes.

DR. SNYDER: Yeah.

DR. BELSITO: Did we leave on formulations?

DR. SNYDER: Yeah. Yeah, that's correct.

DR. BELSITO: And '02, '03, the ingredient was in 178 formulations, up to five percent. Unpublished was received and incorporated into this report. Include human patch test, five-day clinical use assay, clinical use of a serum containing 17.84 percent propylene carbonate. Maximization assay in human skin at 17.84 percent. So, the question is, do we have the data to support the increased frequency and use concentrations? So, looking at this, first of all, impurities. Were we okay with the impurities as recorded? Potentially, impurities include residual carbon dioxide and low molecular weight aldehydes and degradation products.

DR. RETTIE: I was okay with that. It says it's better than 99 percent pure.

DR. BELSITO: Okay. It's used in baby products, but we don't have a concentration. There is some data that it can be irritating. From the original report -- this, I had for you, Allan, in particular -- it says that propylene carbonate may have produced a low level photoallergic reaction in 1 of 25 individuals. I looked at the structure of this; I don't see anything that's going to absorb light.

DR. RETTIE: It's carbon (inaudible) there. Is that why they were focused on phototoxicity?

DR. BELSITO: Would that be a UV absorber? I mean, I thought you needed ring structures, no?

DR. RETTIE: I think you just need biotransition common in carbonate, to my recollection, but I may be wrong. Paul? I'm not familiar with that. Let me consult my photosensitization PowerPoint.

DR. BELSITO: I got carbonyl groups tend to share weak absorbents at 300 nanometers. Yeah, I don't think that -- I mean, if you did Henry's Law, I think that it would not be a concern for photo. I mean, that's the one issue that I had. And we don't have UV absorption.

MS. FIUME: So, on PDF Page 61, it was -- years ago when we first start doing re-reviews, the writer would prepare a full report, and then it was determined whether or not it was opened or not. So, a lot of times it was a lot of work. Then that just went away.

DR. BELSITO: Right.

MS. FIUME: So, we have included the document that was presented to you at that time, so it does say --

DR. SNYDER: Does have a reference. Yeah.

MS. FIUME: But it says that range is not specified, but it had high UV absorption. But it doesn't specify the range.

DR. BELSITO: Got an optical cutoff at 230 to 260. Then we never really discussed why we discounted the potential photoallergy. And does it say, formulated to be nonirritating, or is it, insufficient, we need a UV absorption spectra, is where I ended up. It should be easy enough to get a UV absorption spectra; that doesn't cost a hell of a lot of money.

MS. FIUME: Right.

DR. BELSITO: Paul, Curt, Allan?

DR. SNYDER: I vote whatever everybody else says.

DR. KLAASSEN: I support what you just said. Ask for it.

DR. SNYDER: Yep.

DR. BELSITO: Okay.

DR. RETTIE: Has to be data-driven.

DR. BELSITO: Okay. So, we've got in our discussion respiratory and airbrush technology, the usual. We got a report of photoallergic contact dermatitis. We don't have an absorption study. We don't have other data. Our feeling is that this material is not going to sufficiently absorb light, but in the absence of that, it's hard for us to know. And so, we're going to go insufficient for a UV spec.

And I guess while we're there, I mean, can we ask for concentrations in baby products? And then we just assume that it's the same concentrations as elsewhere. We're going insufficient. Would we like to know that?

DR. SNYDER: Yeah.

DR. KLAASSEN: Let's ask, yeah.

DR. SNYDER: We can ask for it, and then can make a decision whether we need it or not later.

DR. BELSITO: Okay. Anything else in this report? Okay.

Cohen Team – September 30, 2024

DR. COHEN: Propylene carbonate. In 1987, we published a safety assessment on propylene carbonate which functions as a solvent and viscosity decreasing agent with the conclusion that it's safe as a cosmetic in present practices and concentration. The Panel previously considered a re-review in 2004 and reaffirmed that 1987 conclusion published in 2006. It's been 15 years and in March we determined to reopen the report due to increasing frequency in concentration of use. According to the 2023 VCRP propylene carbonate is reported to be used in 882 total formulations with a max concentration of 17.9 percent in leave on formulations.

Cosmetic Direct reported over 17,000 uses. We have HRIPT at max concentration. We have some evidence of irritation. Do we have any data needs or comments?

DR. TILTON: There's actually quite a bit of data that came with this report, and so we have new data on metabolism, dermal penetration, dermal and oral toxicity reproductive toxicity, genotox, carcinogenicity, dermal irritation, ocular irritation. So, I didn't see any needs for additional data.

DR. COHEN: What do you got, David?

DR. ROSS: I got totally wound up with this one.

DR. COHEN: Wrapped around the axel for propylene carbonate.

DR. ROSS: Yeah, and I was going deep into these ECHA documents on the DART developmental and reprotox and in summary I think it's fine.

DR. COHEN: I did not expect that.

DR. ROSS: Well, you know, I mean, the ECHA documents, as you know, they can be a little difficult to interpret but they had some data in there and they actually came up with NOAELs for maternal and developmental tox. We don't quote those. But they also concluded that that there was no reliable data available for toxicity to reproduction for propylene carbonate. And the reason was, I think, was that they didn't have a second species.

So, I think our numbers -- finally I got to the point where our numbers in there are just fine, and I think it's fine as is. And the only other concern I had was the ocular, some of the in vitro tests gave, I think, some significant cause for concern but that was mitigated with the animal tests using neat because there were three tests there with animals using neat material and they were either mildly irritant, moderately irritant, or totally non-irritant. So, on balance I thought safe as used.

DR. COHEN: I had safe as used when formulated to being non-irritating.

DR. ROSS: Okay, I'm willing to go with that.

DR. COHEN: Yeah. It's not going to be my motion tomorrow, but I think one valuable point about this is it's a very important excipient in pediatric ointments for eczema and what's noted in studies using propylene glycols as excipients in drugs like tacrolimus ointment, the vehicle burns and stings in like a fifth of people putting it on.

DR. ROSS: Propylene carbonate or propylene glycol?

DR. COHEN: Carbonate. Propylene carbonate is a critical excipient in tacrolimus ointment, and it's approved down to two years of age with very large surface area of use. So, it's been adjudicated on the drug side and that gave me some comfort because they'd be looking at the excipients over large body surface areas for eczema.

DR. ROSS: And it's a FDA approved and active product in topical ointments up to three grams per day.

DR. COHEN: Yeah, and I think that's the very issue at hand is that we really do use it regularly on large body surface areas of two and three-year olds and we do use it for years and years at a time daily and twice daily. So, okay.

DR. ROSS: I'm fine with your amendment.

DR. COHEN: Okay.

DR. TILTON: I also support it.

DR. COHEN: Good. Thank you. I think that's a wrap. Any comments or advice for tomorrow? Wilma, any?

DR. BERGFELD: No. I think that we've discussed some of the points that were a little iffy and if they're said succinctly, I think we'll be fine.

DR. COHEN: Pithy, right?

DR. ROSS: Pithy.

DR. COHEN: We're going to need pithy reviews tomorrow.

DR. ROSS: Pithy and palaver.

DR. COHEN: Okay, thank you for all participating.

DR. BERGFELD: We'll see you tomorrow virtually?

DR. COHEN: I'll see you all virtually and I think the virtual link is in the calendar, I think.

DR. HELDRETH: There's one for today and one for tomorrow.

DR. COHEN: All right, so we're adjourned.

Full Team – October 1, 2024

DR. BELSITO: Yeah. So, in '87, we published a safety assessment with a conclusion that Propylene Carbonate is safe as a cosmetic ingredient in the present practice of use. This was re-reviewed in 2004 and was reaffirmed. It's been 15 years. So, we're going on to do another re-review. In March of 2023, we did reopen the report because of increased frequency and concentration of use, specifically up to 17.9 percent concentration of use in leave-on products.

And unpublished data has been received and incorporated into the report, including human patch tests five-day clinical use assay and clinical use tests at 17.84 percent Propylene Carbonate. And, based upon that, we thought we could go with a safe as used conclusion.

DR. BERGFELD: So, that's a motion. Is there a second for safe?

DR. BELSITO: Oh, excuse me. I'm sorry.

DR. BERGFELD: Don.

DR. BELSITO: Pull back. We were concerned about the report of one out of 25 photo allergic responses. And we're actually going insufficient for UV absorption.

DR. BERGFELD: Okay.

DR. BELSITO: We don't think it will absorb, but we would like the UV spect.

DR. COHEN: Okay.

DR. BERGFELD: Excuse me. Wait a minute. Wait a minute. We had a motion of safe. We had it seconded. David, can you rescind?

DR. COHEN: No.

DR. BELSITO: We didn't second it.

DR. COHEN: I didn't second it.

DR. BELSITO: I corrected my --

DR. BERGFELD: You corrected just now?

DR. BELSITO: Yeah.

DR. BERGFELD: Okay. We're into comments. All right. So, insufficient is the motion. Is there a second?

DR. COHEN: A second. So, Don, that's good pick up. And the question I was going to have for you was, in the report, there's descriptions of irritation. It may not be irritant dermatitis, but there's sensory irritation from propylene carbonate.

We have it in the report, and we have it in our experience with pharmaceutical products that have it and when it's in the placebo. So we were -- would think about, you know, if and when you get your data, safe when formulated to be nonirritating.

DR. BELSITO: Yeah. That's what I originally had.

DR. COHEN: Oh, that was in your motion. I didn't hear that. I'm sorry.

DR. BERGFELD: No. He didn't say it.

DR. BELSITO: I didn't get to that part when Paul reminded me that we had insufficient data.

DR. COHEN: Okay. So let's go with your IDA. And, when it swings back around, we can make the final determination.

DR. BELSITO: Right.

DR. BERGFELD: Okay. And, so, you're seconding the insufficient?

DR. COHEN: Yes.

DR. BERGFELD: And the comment is we're going for insufficient UVA. And then, the other comment is, when that is received, it may be considered safe --

DR. BELSITO: When formulated to be nonirritating.

DR. BERGFELD: Nonirritating. Okay. Got it.

DR. BELSITO: I mean, the UV spect should be easy enough to provide on this.

DR. BERGFELD: Okay.

DR. BELSITO: And I think it will clear it. I don't think it's going to absorb. But we have this one bit of data there, and we don't know whether it's a photosensitizer or not.

DR. COHEN: Don, for (inaudible) adjoinment for pediatric and adult use, wouldn't they have needed a photosensitivity workup for the FDA dossier and a phototox? Propylene Carbonate is an excipient in (inaudible) adjoinment for children on both formulations. That's why I didn't get too caught up on it. But I'm okay with the IDA and seeing what comes of it. But I would've expected the drug dossier to require it. But maybe you're right.

DR. BELSITO: I don't recall.

DR. COHEN: Okay. Well, we'll see what comes back.

DR. BERGFELD: All right. Any other comments before we take the vote?

DR. HELDRETH: I think Priya has a question or comment.

MS. CHERIAN: Yes. Yesterday in Dr. Belsito's team, I think one of the requests was also concentrations of use in baby products. Would you like to add that to the IDA?

DR. BELSITO: Yes, we did ask for that. Thank you, Priya.

MS. CHERIAN: You're welcome.

DR. BELSITO: We have reports of use in baby products with no concentration. So, since we're going for an IDA, we thought we could ask for that.

DR. BERGFELD: Okay. So that has been added. Any other? So, I think we've come to the conclusion, and can we call for a vote, even if it's a second vote. It's been very confusing here.

DR. BELSITO: There's been no vote.

DR. BERGFELD: I know. All those in favor of insufficient with two items, and that is the UV and the baby? All right. Thank you. Unanimous. All right. All right. Moving on to other items, 2-Bromo-2-Nitro-1,3-Propanediol, Dr. Cohen.

MARCH 2025 MEETING – DRAFT TENTATIVE AMENDED REPORT/ SECOND REVIEW

Belsito Team – March 13, 2025

DR. SNYDER: Propylene carbonate is next. This is a tentative amended report. In September of 2024, we issued an Insufficient Data Announcement. We wanted the concentration of use in baby products and UV absorption data. And, if it was absorbed, then we needed phototox and photosensitization data. We've received no new data. There's been new RLD data incorporated. It's used in over 13,000 formulations. The highest concentration of leave-on is 17.9 percent. Let's see, 1987, report was published.

It was re-reviewed in 2006 and 2023. 2023, was reopened due to increased use and concentration of use. And then, there were PCPC comments, Page 15 on Wave 2, regarding UV absorption and the 13-week rat inhalation study in support of inhalation safety. So, that's where we're at.

DR. BELSITO: So, that PCPC comment, it was the Grisig (phonetic) paper. And, basically, this lacks a chromophore functional group, and so it's not going to absorb. Right? I mean, that was the basis of that paper, which I can forward to you. I mean, there's no absorption in the UV region. So, I'm not sure where the photo came in.

DR. RETTIE: Well, the one I'm reading says there's no absorption in the UV region between 240 and 340 nanometers. They seem to specify. Phototoxic drugs, as you know, could have significant absorbance slightly above that, up to about 380.

DR. BELSITO: Yeah. I mean, they can go into UVA. I agree, but where are you seeing that data?

DR. RETTIE: Yeah. I'm referring to the Wave 2 comments about UV transparency. They provide a reference in Wave 2.

DR. BELSITO: Right, the Grisig paper.

DR. RETTIE: That's not the one that I think is actually the reference. I think the reference is the Fujinaga (phonetic) paper. I think that might be a source of confusion.

DR. BELSITO: Which paper, Allan? I'm sorry.

DR. RETTIE: There's a paper by Fujinaga and Izutsu (phonetic).

DR. SNYDER: Where's that at? I don't see that in here.

DR. RETTIE: I did dig for this. So, it may not be in here.

DR. BELSITO: Because the Grisig paper basically claims this has no photo absorptive capabilities.

DR. RETTIE: Yeah. I think we can agree that the phototoxicity here is kind of a red herring. We don't really need it.

DR. BELSITO: If you look at the structure of this, Allan, would you predict it to absorb?

DR. RETTIE: I wouldn't. There's no aromatic groups. That's the first place you'd look.

DR. BELSITO: Right.

DR. RETTIE: But there's actually a reference out of there that I think is not the reference that we're talking about right now that says it's UV transparent.

DR. BELSITO: Right.

DR. RETTIE: Have you found that Fujinaga reference, Priya?

DR. BELSITO: What's the Grisig reference? It says it's transparent in the UV region and it references Reference 16 in that paper. I can tell you in a second with that reference. And it lacks chromophore potential which, if you look at the structure of the molecule, it clearly does.

DR. RETTIE: Agreed.

DR. BELSITO: Reference 16 in the Grisig paper, is that's where you got the Fujinaga and Izutsu, Allan, is 16 in that paper?

DR. RETTIE: Correct. Yep.

DR. BELSITO: Propylene carbonate purification and test for purity, I didn't look at that paper. Did it say that it absorbed?

DR. RETTIE: It did not.

DR. BELSITO: Right. So, I don't think it has photo potential.

DR. RETTIE: I don't think so either. I think we should reference the right reference, though, if we have them.

DR. BELSITO: Yeah. We have two references.

DR. RETTIE: I think the prime reference is the Fujinaga one.

DR. BELSITO: I would agree.

DR. SNYDER: Where's that listed, that Fujinaga one?

DR. BELSITO: You have to go to the Grisig paper, which is not here.

DR. SNYDER: Oh, okay.

DR. BELSITO: And it's R16 in the Grisig paper. It's Fujinaga and Izutsu. It's from Pure Applied Chemistry. It's a 1971 publication.

DR. SNYDER: Okay. So we have a reason why we don't need that.

DR. RETTIE: Yeah.

DR. BELSITO: We have two reasons. If you look at the chemical structure, you would predict it won't absorb.

DR. SNYDER: And then those references.

DR. BELSITO: Exactly. I thought it was safe as used. There's all rinse-off except one very questionable leave-on, and how did you determine that other category was leave-on? And the only concern I could see with baby products would be irritation.

DR. RETTIE: I have a note. We have no dose and no concentration for the baby products. Is that right?

DR. BELSITO: But then we assume the max concentration would be what the max concentration is in other uses. Right?

DR. SNYDER: Yeah.

DR. RETTIE: Yep. Okay.

DR. BELSITO: I mean, safe as used, formulated to be non-irritating if you are concerned at all. But not even sure that there's maybe irritation data. 100 percent concentration, oh, very high concentrations.

DR. SNYDER: Yeah. very high.

DR. BELSITO: But 100 percent non-irritating in rabbits. 100 percent, 18 human subjects, primary irritation is low. No significant difference between test material and reference. I mean, I don't even think you need to put an irritation restriction here.

DR. SNYDER: Okay. I agree. Safe as used.

DR. RETTIE: A minor point to consider in the composition synthesis section. There's a lot of information there.

DR. SNYDER: What page are you on?

DR. RETTIE: I'm trying to find it. PDF 21. PDF 22, sorry, Method of Manufacture. Yeah. I wondered if we could reference something rather than the phosgene synthesis. That's actually new information, non-italics, in paragraph three, because unless you're a (inaudible) chemist, you're not going to work with phosgene. And there's just literally a laundry list of alternative ways to make this. I found a really nice -- I could send that to you, Priya -- a really nice figure. Modern methods probably don't use phosgene.

MS. CHERIAN: Sorry to go back, but where did you see the incorrect reference for UV absorption?

DR. RETTIE: This was in the Wave 2 comments that were provided to persuade us that it was a red herring.

MS. CHERIAN: Okay.

DR. RETTIE: They reference an article that referenced the real thing.

MS. CHERIAN: I understand. Okay. I was looking for the reference in here.

DR. RETTIE: No. You gotta dig.

MS. CHERIAN: Okay. Got it.

MS. FIUME: Can I also take it back a step as well? Don, I thought I heard that these are all rinse-off.

DR. SNYDER: The majority are, he said.

DR. BELSITO: Well, they're all rinse-offs, except there was a question for leave-on. I think it said questionable LO. And I just was wondering how you determined that other category was leave-on.

MS. FIUME: So, the use table indicates 874 leave-ons. Right? Am I looking at it wrong?

DR. BELSITO: Maybe I was looking at it wrong.

MS. FIUME: Yeah. For VCRP, Table 2 is PDF Page 29.

DR. BELSITO: Uh-huh.

MS. FIUME: There were, in the VCRP, 874 leave-on, 8 rinse-off in 2023.

DR. BELSITO: But in the RLD --

MS. FIUME: We don't break those out yet because we really aren't sure how to categorize them.

DR. BELSITO: Okay.

MS. FIUME: So, we don't have leave on and rinse off. Oh, the other baby product. Is that what you're looking at is the other baby product that was a leave-on?

DR. BELSITO: Yes, I'm sorry. Yeah.

MS. FIUME: So, that is based on the information that comes in the RLD, it will indicate that it's a leave-on.

DR. BELSITO: Okay. I totally misread that table.

MS. FIUME: Okay.

DR. BELSITO: I apologize. So, then, maybe our conclusion would be better safe as used when formulated to be nonirritating.

DR. SNYDER: But I thought you just said we had 100 percent nonirritating in rabbits and clinical data all negative, so we didn't need that.

DR. BELSITO: Yeah. I mean, I guess we don't.

DR. SNYDER: Yeah. Okay. I agree.

DR. BELSITO: Okay. Safe as used, then get rid of the nonirritating.

DR. SNYDER: Okay. Thank you. Good discussion as always. Sometimes we go around in circles, but we always get there.

MS. FIUME: We get there.

DR. SNYDER: We always get there.

CohenTeam – March 13, 2025

DR. DAVID COHEN: So we have a Draft Tentative Amended Report on the safety of Propylene Carbonate.

In September, the Panel determined the data were insufficient to support safety of the ingredient. We issued an IDA asking for concentration of use in baby products and UV absorption data. And if there was absorption data, that was important. We'd ask for phototox, photosensitization. Since the IDA was issued, we've received no new data. We've received some -- we have RDL that's been incorporated into reporting Propylene Carbonate is used in over 13,000 formulations.

All right. Listen, I'll throw it back. I think we asked for some of this information. I think there was some additional material that came in for us just to think about. I think it was for Propylene Carbonate and it's potential to be photo-absorbing. But, Susan, you want to start with your thoughts?

DR. TILTON: Yes. So when we discussed this -- when was it? We discussed the draft report in September. We were provided with quite a bit of toxicity data. I would say Propylene Carbonate has a pretty complete set of toxicity report data, not really a lot of concerns with regard to toxicity. So we were focused primarily on requesting the UV absorption data, concentration in baby products. We did not get any concentration in baby products.

I would say, even though we don't have concentrations, based on the toxicity data that we have, I don't have a lot of concerns. I think, of the products that are reported in the RLD, majority of them are rinse-off products. And we do not have -- going back

through the toxicity data that was provided that we discussed in September, I really don't have a lot of concern with regard to its use there. We did not get new data, although I do think in the Wave 2 PCPC did provide data on UV spectra.

DR. DAVID COHEN: Yes. It was good information.

DR. TILTON: Suggesting it might be absorbed in the lower range. Is that correct? Do we have that correct?

DR. ROSS: Yeah, it was 220.

DR. TILTON: At about 220.

DR. BERGFELD: Did you refer to the higher concentration? It was close to 18 percent, which appeared in something, night moisturizer, I guess.

DR. ROSS: Derma leave-on. Yeah.

DR. DAVID COHEN: In a leave-on.

DR. BERGFELD: Yeah.

DR. TILTON: From the new report.

DR. DAVID COHEN: Propylene carbonate is a, I think, pretty commonly used pharmaceutical excipient. It's very well studied.

DR. BERGFELD: Have you seen any problem with it?

DR. DAVID COHEN: Burning and stinging.

DR. BERGFELD: Oh, but that's the burning and stinging?

DR. DAVID COHEN: Tacrolimus ointment has got it. And so even the placebo tacrolimus --

DR. BERGFELD: The (inaudible) does that without a reaction?

DR. DAVID COHEN: -- has burning and stinging. Yeah.

DR. BERGFELD: Um-hmm. I knew that.

DR. DAVID COHEN: So okay. Sam?

DR. SAMUEL COHEN: The only thing I had some confusion on was that it was listed at sensory no irritation on skin up to 20 percent. And ocular was up to 17.5 percent. So which one do you use as accepted?

DR. BERGFELD: It's both.

DR. DAVID COHEN: What was the question?

DR. SAMUEL COHEN: The skin irritation was up to 20 percent, and ocular irritation was up to 17.5 percent, so this is basically the same. But which one do you use as a limiting?

DR. DAVID COHEN: Again, just contextualize it for where it's being used.

DR. SAMUEL COHEN: Okay.

DR. DAVID COHEN: It looks like in eye areas, 2.7 percent.

DR. ROSS: 2.7 percent. Yeah.

DR. DAVID COHEN: 2.7, yeah. So you have a big margin there. David?

DR. ROSS: Yeah. The IDA was based on a couple of concerns. One was the phototoxicity, and the other was the no concentrations for baby product use. I agree with Susan, pretty much no genotox concerns with this material. I actually originally didn't have too many concerns with phototoxicity.

DR. DAVID COHEN: No, we originally didn't.

DR. ROSS: And also, the nice PCPC comment on the UV cutoff. Thank you very much.

DR. DAVID COHEN: Yes.

DR. ROSS: That helped out a lot. No baby product concentrations have been received as Susan pointed out. We've still got some very small number of uses in the RLD in baby products, so I think that's a question for us.

Our document, if we get there, will still approve at 17.9 percent, theoretically, if we approve it. And so if we approve it like that, I mean, theoretically, you could still use 17.9 percent in baby products, I guess. So you're going to have to -- it's a very

small number of uses, but it's something for us to consider. An original concern of mine was ocular, because there was some very varied data in this dossier.

DR. DAVID COHEN: Yes.

DR. ROSS: The older rabbit studies need concentrations. Three studies were either non-irritating, moderately irritating, or light edema. The newer in vitro data, the porcine opacity test and the HET-CAM data, indicated 15 to 25 percent was damaging. The eye max concentration is quite low. It's 2.7 percent in ocular products.

But if you look at the number of uses from the RLD, if I'm reading this right -- and someone correct me if I'm wrong -- it's something like 2500 uses out of 13,000 in ocular products.

DR. DAVID COHEN: And to me, just from a very practical standpoint, a baby shampoo is an ocular exposure.

DR. ROSS: Okay.

DR. DAVID COHEN: They're intrinsically ocular exposures. So I was good with safe as used. And then I get stuck with, we don't have the concentration in baby products, right? Doesn't stop us from clearing it, but does it force the --

DR. ROSS: Irritating?

DR. DAVID COHEN: Does it force us to be formulated when not irritating?

DR. ROSS: That's what I wonder too.

DR. DAVID COHEN: Is it an unforced error on industry part where, you know, I don't have baby formulations. I expect baby shampoo to wind up on the face, nostrils, and lips of babies, right? It's just you can't do it any other way. So then is this the tag that gets added on?

DR. ROSS: Yeah, that's where I argue with myself around because I hate to use these caveats, these get-out-of-jail cards, right?

DR. DAVID COHEN: Yeah. I know.

DR. ROSS: When I joined this Panel, it was this beautiful comment by Ron Shank, previous toxicologist on this Panel, and he responded to a comment and said, well, why don't we just say when formulated to be nontoxic, and then we can all go home? So I kind of like that.

DR. DAVID COHEN: He was amazing.

DR. ROSS: But, no, I think we might be there with this one when formulated to be nonirritating. We've got the ocular concentration issue, but we've particularly got the baby concentration issue.

DR. DAVID COHEN: Right, because the ocular concentration is 2.7 percent, but if you have it at 15 percent in a baby shampoo, your ocular concentration is higher.

DR. SAMUEL COHEN: Yeah. Yeah.

DR. BERGFELD: In a rinse-off?

DR. DAVID COHEN: Huh?

DR. BERGFELD: In a rinse-off.

DR. ROSS: In a rinse-off. Yeah.

DR. DAVID COHEN: In a rinse-off, right? But when you're rinsing babies, you're usually not putting them in a face wash. You know what I mean?

DR. HELDRETH: You do have the option of posting an insufficiency for that concentration of use in baby products.

DR. ROSS: Yeah. That's right.

DR. DAVID COHEN: You mean continuing the insufficiency?

DR. HELDRETH: Okay, so I'm trying to remember what we had before.

DR. BERGFELD: You could also treat it like you're treating the last ingredient to put it in the Discussion with a range of concentrations and describe the baby?

DR. DAVID COHEN: We actually don't have data on it. We're just extrapolating.

DR. BERGFELD: Well, you have a range of use up to 18 percent, I mean, in that one product line, the one, the night, whatever it is, moisturizer, I guess.

DR. HELDRETH: Okay. So I see what you're saying. Yes, so you already asked for that. You didn't get that.

DR. DAVID COHEN: That's right.

DR. HELDRETH: It could be part of your conclusion insufficient in baby products.

DR. ROSS: I don't think we need to go insufficient on this. I mean, there's a lot of data in here.

DR. BERGFELD: It's saying nonirritating up there.

DR. SAMUEL COHEN: Do we have any data? I noticed that you mentioned it earlier that this is used as an excipient for a number of products.

DR. DAVID COHEN: Actually, it's approved for two-year-olds.

DR. SAMUEL COHEN: Yeah. So do we have any data from there as to what the exposure is there? And does that give us some useful data that we can use here?

DR. DAVID COHEN: It does.

DR. SAMUEL COHEN: I don't know the levels.

DR. DAVID COHEN: It's approved in pharmaceutical product for atopic dermatitis used on the face for two years of age and above. And there are our national guidelines of care which suggest its use into infancy and facial products.

DR. BERGFELD: But there's an acceptable burning/stinging with it.

DR. DAVID COHEN: There is burning and stinging with it, right? But it's a pharmaceutical product with appropriate warnings. This is not that, right? So you're bringing us back, right? That gets back to formulated to be non-irritating.

DR. BERGFELD: Right.

DR. TILTON: I mean, I would support formulated to be non-irritating. But I will note that the 17.9 percent is in the leave-on moisturizer. So the highest concentration in rinse-off products is listed at 6 percent. So that's why we would essentially be assuming in present use and practice for a baby shampoo, I guess, would be a highest concentration of 6 percent, not 18 percent.

DR. DAVID COHEN: Well, so that's a good point. So what you're saying is now, instead of locking in down low, you're going up to a domain. The domain is rinse-off or leave on. That's the domain. And then the items within the domain are the specific products.

So this is a different discussion. Are you locked into a domain and saying, rinse-off products of all sorts should be no higher than 6 percent, right? Forget what's used in a shampoo or a body wash. It's a rinse-off product. I mean, it's a rhetorical question, so I don't expect an answer.

DR. ROSS: Gets back to this whole present practices of use thing.

DR. DAVID COHEN: Which we never had a problem with until today.

DR. ROSS: Yeah. It's a global definition in these reports. And I'm probably the one that's argued against it most, but I'm coming to see the value of it now because we got a lot of different ranges of concentrations in different products as you point out. And if it's not in the report, we're not approving it because it's not present practices of use.

DR. DAVID COHEN: We could just put it in the Discussion. Are we formulating it to be nonirritating?

DR. BERGFELD: Absolutely.

DR. ROSS: I mean, with the baby usage and then --and I think you could probably clear on ocular because it's a lower percentage. But we actually don't have the data, so we don't have HET-CAM data at 2, 3 percent. We've got irritation in the in vitro tests at 15, 25 percent. That's still way higher. But we actually have no data on ocular lower. So I think when formulated to be nonirritating is fine for me.

DR. DAVID COHEN: Okay. And I thought the second wave -- well, I didn't think we had a high suspicion of UV absorption based on the formulation, right? There are no carbonyl, nitrile, azo groups.

I don't know. I can't remember why we got -- I think there may have been one suggestion in one report. But I think the information that we got in the second wave kind of (inaudible). I was fine with it at that point.

DR. ROSS: Yeah. I think that was Don's point. Yeah. Just another point, we didn't have a margin of exposure in here, which just underlines we don't always have to do one.

DR. DAVID COHEN: Okay. So are we aligned with safe as used when formulated to be nonirritating?

DR. ROSS: Yes.

Full Panel – March 14, 2025

DR. DAVID COHEN: Thank you. This is a Draft Tentative Amended Report on the safety of Propylene Carbonate. At the September 2024 meeting the Panel determined that the data were insufficient to support the safety. And we issued an IDA with the following data needs: concentration of use in baby products, and UV absorption data.

Since the IDA was issued, the CIR received no new data. However, RLD submitted in 2024 has been incorporated into the report indicating over 13,000 formulations containing the product. I'll go right to a motion of, and we can have a discussion after, safe when formulated to be nonirritating.

DR. BERGFELD: Second.

DR. SNYDER: Belsito Team, seconds.

DR. BERGFELD: Any other discussion regarding this ingredient? Dr. Cohen, do you want to say something else?

DR. DAVID COHEN: Add there were no baby product concentrations, but I think --

DR. BERGFELD: Is that in the Discussion? Are you putting that in the Discussion?

DR. DAVID COHEN: It ought to be. Yes, it is to be in the Discussion is my second point.

DR. BERGFELD: Anything else? All right. I'll call the question.

DR. BELSITO: Yes, we needed clarification on UV absorption. And there was a paper that PCPC refer to, Grisig (phonetic) paper. But the Grisig paper then refers to a paper by Japanese authors, and we thought those should be brought into the document to show that -- first of all there's no chromophore, so the idea that this would absorb was sort of funny. But the studies also show that it doesn't absorb and UV for that range.

DR. DAVID COHEN: Yes, we could --

DR. BELSITO: So, just to bring those in.

DR. DAVID COHEN: That's great. We agree.

MS. CHERIAN: I had a quick question for the Discussion. There is a Council comment asking if we can use the chronic -- it was sub-chronic or chronic -- inhalation toxicity study in the Discussion. It's kind of a general question because I've done it both ways. We've discussed a specific study in the Discussion section instead of just the boilerplate language. If we have inhalation toxicity, should we discuss that in the Discussion, with the boilerplate language that we have now?

DR. BERGFELD: Any comment on the inhalation discussion in the Discussion portion of the document.

DR. DAVID COHEN: Susan, David, you want to comment on that?

DR. TILTON: Yes, if we have data we should include it in the Discussion with the boilerplate.

DR. BERGFELD: Okay.

DR. SNYDER: The Belsito Team would agree. And so, as Don alluded to earlier, we want to report all the data that we have. And we can address it as to how we interpreted it or to how we dealt with it. I think that's appropriate to do that, Priya, like you said, in addition to the inhalation boilerplate. Thank you for bringing that up.

DR. BERGFELD: All right, I'm going to call the question then, since there is no further discussion. All those in favor of the conclusion safe raise your hands please. Unanimous again. Moving on to the next ingredient, Dr. Snyder presenting, Trimethylbenzoyl Diphenylphosphine Oxide.

OCTOBER 1994 MEETING – INITIAL REVIEW/ORIGINAL DRAFT REPORT

October 4 – 5, 1984 Panel Meeting Summary

Dr. Bergfeld recommended an Insufficient Data Announcement be issued due to the lack of mutagenicity studies on Propylene Carbonate.

The Panel unanimously accepted and approved the following statement:

The Expert Panel requests:

Mutagenicity data for Propylene Carbonate, Ames-Preincubation Test (or Modified Ames Test) with and without S9 mix and at various pH, would be meaningful for estimating the genotoxic activity of this cosmetic ingredient.

It is possible that Propylene Carbonate could come in contact with the oral cavity (saliva pH 5.7 - 6.4), stomach (juice [women] -2.6), skin (sweat 4.0- 6.8) and blood (7.2- 7.4). Thus, Propylene Carbonate must be bioassayed in buffered solutions at pH -2.6, -4.0, -6 and -7.3.

Propylene Carbonate will decompose in systems which vary significantly from neutral pH. The resulting decomposition products may be alkylating agents and therefore may be genotoxic. The Ames assay, completed at various pH, should result in data which indicate if reactive species are formed during the decomposition of Propylene Carbonate at various pH.

The Insufficient Data Announcement will shortly be issued for a 90-day public comment period.

NOVEMBER 1985 PANEL MEETING – SECOND REVIEW/ORIGINAL DRAFT TENTATIVE REPORT

November 25, 1985 Panel Meeting Summary

Dr. Bergfeld reported that the Panel had issued on IDA October 10, 1984, requesting mutagenicity data (modified Ames assay) on Propylene Carbonate and that a submission of data had just been received. These data included mutagenicity and additional animal toxicity studies and had not been incorporated into the report. She reported that Dr. Hoffmann had reviewed and summarized the mutagenicity and genotoxicity studies the previous evening. Her team, after reading Dr. Hoffmann's summary, and after Dr. Hoffmann had called the researcher who conducted the study, had agreed that the mutagenicity data were adequate. At that point, Dr. Hoffmann read his summary of the mutagenicity data to the Panel.

Dr. Bergfeld noted that some of the data submitted were on experimental products containing up to 20% Propylene Carbonate; results of these studies (oral toxicity and skin irritation) had shown the products to be highly toxic and irritating. However, as Propylene Carbonate is only used in cosmetics at concentrations up to 5%, her team felt it important to clarify in the discussion that 20% was not a use concentration. Some discussion ensued as to whether it was sufficient to not this in the discussion or if the "safe" conclusion should be limited to a concentration of ≤ 5%.

Mr. Eirmann questioned that the sole cosmetic use of Propylene Carbonate was as a polar additive for clay gellants. It was noted that this information came from CTFA and would be rechecked.

Dr. Shank raised a question regarding the carcinogenicity of propylene oxide, a decomposition product of Propylene Carbonate (noted in a footnote of page 2). He questioned the rates and/or amounts of decomposition to propylene oxide. Dr. Hoffmann indicated that the carcinogenicity noted was seen in a subcutaneous injection study in rats, which is not considered a definitive study for carcinogenicity. Dr. Hoffmann stated that he would check the study and call CIR to confirm. It was also noted that the report should document that the Panel had considered the decomposition products of this ingredient.

Dr. Bergfeld then recommended the standard "safe" conclusion for Propylene Carbonate with the documentation in the discussion of the 20% studies versus the 5% use concentration. She requested that the Panel vote on this recommendation and have a mail review in that the new data had not been incorporated into the report nor had it been seen by the other Panel members.

The Panel unanimously accepted and approved the standard "safe" conclusion as recommended by the Bergfeld team.

The Tentative Final Report will shortly be sent out for a mail review by the Panel

SEPTEMBER 2004 PANEL MEETING – FIRST RE-REVIEW

September 9 – 10, 2004 Panel Meeting Summary

Dr. Marks stated that a Final Report with the following conclusion was published in 1987: On the basis of the available data, the CIR Panel concludes that Propylene Carbonate is safe as a cosmetic ingredient in the present practices of use and concentration. After reviewing data that have entered the published literature since the Final Report was issued, he noted that his Team determined that the Final Report should not be reopened.

Dr. Belsito thanked Bill Brock for providing the unpublished data that are included in the re-review report.

The Panel unanimously concluded that the Final Report on Propylene Carbonate should not be reopened.

Amended Safety Assessment of Propylene Carbonate as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
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ABBREVIATIONS

CIR	Cosmetic Ingredient Review
CLP	classification, labeling, and packaging
CMC	carboxymethylcellulose
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DART	developmental and reproductive toxicity
EC	European Commission
EC_{90}	estimated concentration of what causes effects indicative of serious eye damage within 90 s
ECHA	European Chemicals Agency
FDA	Food and Drug Administration
FOU	frequency of use
GHS	globally harmonized system
HET-CAM	hen's egg chorioallantoic membrane
LD_{50}	median lethal dose
LLNA	local lymph node assay
l.o.	leave-on
LOAEC	lowest-observed-adverse-effect-concentration
LOAEL	lowest-observed-adverse-effect-level
MoCRA	Modernization of Cosmetics Regulation Act
MW	molecular weight
NOAEC	no-observed-adverse-effect-concentration
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
RLD	Registration and Listing Data
r.o.	rinse-off
SIOPT	single-insult occlusive patch test
TCA	trichloroacetic acid
TG	test guideline
US	United States
UV	ultraviolet
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of Propylene Carbonate, which is reported to function as a solvent and viscosity-decreasing agent in cosmetic products. The Panel reviewed the available data to determine the safety of this ingredient. The Panel issued an amended report with a revised conclusion stating Propylene Carbonate is safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

INTRODUCTION

Propylene Carbonate is an organic compound that, according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), is reported to function in cosmetics as a solvent and viscosity-decreasing agent.[1] This ingredient was previously reviewed by the Panel in a report published in 1987.[2] At that time, the Panel concluded that Propylene Carbonate is safe as a cosmetic ingredient in the present practices of use and concentration described in that report. The Panel first considered a re-review of this report in September 2004 and re-affirmed the original conclusion, as published in 2006.[3] In accordance with its Procedures, the Panel evaluates the conclusions of previously issued reports every 15 years, and as it had been at least 15 years since the previous re-review was issued; accordingly, the Panel again considered a re-review of this ingredient at the March 2023 meeting. At that meeting, the Panel determined that this safety assessment should be re-opened due to increased frequency and concentration of use.

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 in May 2025 for studies published in 2003 onwards. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the summaries of the 1987 report are disseminated throughout the text of this document, as appropriate, as are excerpts of the original re-review document[4] considered by the Panel in September 2004; these data are identified by *italicized text*. (This information is not included in the tables or the Summary section). For complete and detailed information, the original 1987 report can be accessed on the CIR website (https://cir-reports.cir-safety.org/).

It should be noted that propylene glycol, a metabolite of Propylene Carbonate, has been previously reviewed by the Panel. Propylene glycol was determined to be safe as used in cosmetics in the present practices of use and concentration described in that safety assessment when formulated to be non-irritating (as published in 2012).[5]

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[6] 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. In addition, it should be noted that data on a read-across ingredient, propylene glycol, were included in the ECHA dossier. However, since data for the relevant endpoints were found on Propylene Carbonate and are included herein, data on propylene glycol that were summarized in the ECHA dossier are not included in this CIR safety assessment.

CHEMISTRY

Definition and Structure

According to the *Dictionary*, Propylene Carbonate (CAS No. 108-32-7) is the heterocyclic organic carbonate ester that conforms to the structure in Figure 1.[1 CIR Staff]

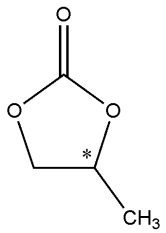

Figure 1. Propylene Carbonate

Propylene Carbonate is a polar aprotic substance with similar characteristics to other organic solvents such as acetonitrile and acetone.[7] While this ingredient has a chiral center (* in Figure 1), Propylene Carbonate is commonly used as a racemic mixture.

Chemical Properties

Chemical properties for Propylene Carbonate (molecular weight (MW) = 102.09 g/mol) are summarized in Table 1.[2,6,8] This ingredient is an odorless, clear liquid, that is partially soluble in water (solubility is increased via the presence of a perchlorate ion).[2] The log K_{ow} is estimated to be -0.41.[6]

Method of Manufacture

Propylene Carbonate is manufactured by reacting propylene oxide and carbon dioxide in the presence of a proprietary catalyst.[2] No purification steps are taken as the reaction product is at least 99% pure.

Propylene Carbonate was reported, by one cosmetic ingredient manufacturer, to be synthesized from propylene oxide and carbon dioxide under supercritical conditions in the presence of a small amount of dimethylformamide.[4] A supercritical carbon dioxide-ionic liquid biphasic system was applied to the carbon dioxide fixation as it may be used as a prominent acid-base catalyst and reaction media.

The following methods of manufacturing are general to the processing of Propylene Carbonate, and it is unknown whether these methods are used in the manufacturing of cosmetic ingredients. On an industrial scale, Propylene Carbonate is typically synthesized through the carboxylation of propylene oxide.[9] Additionally, Propylene Carbonate has also been reported to be synthesized via oxidative carboxylation of olefins using propylene, carbon dioxide, and an oxidant used as substrates, the reaction between a halohydrin, propan-1,2-diol, and dimethyl carbonate, and via urea alcoholysis (using metals, metal ions, metal salts, modified hydroxyapatites, or ionic liquids as catalysts).

Impurities

Potential impurities of Propylene Carbonate include residual carbon dioxide and low molecular weight aldehydes and degradation products.[2] According to a method of manufacture, when reacting propylene oxide and carbon dioxide in the presence of a proprietary catalyst to produce Propylene Carbonate, the reaction product is at least 99% pure.

Ultraviolet (UV) Absorption

The UV cutoff for Propylene Carbonate is reported to be 220 nm.[10] However, it should be noted that Propylene Carbonate is transparent in the UV region, and lacks a chromophore functional group.[11,12]

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 Propylene Carbonate in cosmetics. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was discontinued in 2023 and, as of 2024, manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. However, to utilize the exemption, the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products are not included in this exemption.[13] Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting). Although the VCRP program is now defunct, trends in frequency of use from the RLD alone are not yet possible in that a baseline is currently not available.

RLD submitted in 2024 indicate that Propylene Carbonate is used in 13,340 total formulations (Table 2).[14] According to 2023 VCRP survey data, Propylene Carbonate was reported to be used in 882 formulations (874 leave-on formulations and 8 rinse-off formulations).[15] The results of the concentration of use survey conducted by the Council in 2022 indicate that Propylene Carbonate is used at up to 17.9% in leave-on formulations (skin care preparations – night (not spray)).[16] In 2002/2003, this ingredient was reported to be used in 178 formulations, at up to 5% (in underarm deodorants).[3]

Propylene Carbonate is used in baby products (concentration not reported), products used near the eyes (e.g., in eyeliner at up to 2.7%), and children's makeup preparations (concentration not reported). In addition, Propylene Carbonate may be incidentally ingested as it is used in lipstick formulations at up to 3.9%.

Propylene Carbonate is used in cosmetic sprays and powders, and could possibly be inhaled (e.g., foot powders and sprays at up to 0.28%, deodorant sprays and face powders, both at up to 1.4%). 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 cosmetic sprays 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. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable. However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. 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 Propylene Carbonate are marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined by the FDA, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available in some instances. Some of the reported product categories for this ingredient as listed in RLD do require designation if airbrush application is used, and this type of application was reported (e.g., foundations). Additionally, the Council currently surveys the cosmetic industry for maximum reported use concentrations of ingredients in products which may be used in conjunction with an airbrush delivery system; thus, this type of data may also be available when submitted. Please note that no concentration of use data were provided indicating airbrush application. Nevertheless, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

Propylene Carbonate is not restricted from use in any way under the rules governing cosmetic products in the European Union.[17]

Non-Cosmetic

Propylene Carbonate is used as a solvent in various industries (e.g., electrochemistry), as a plasticizer, as a reaction medium, and in the organic synthesis of other materials.[2] Propylene Carbonate is used as a vehicle in ointments and creams.

This ingredient is an FDA-approved inactive ingredient in topical ointment drug products at a maximum daily exposure dose of 3000 mg.[18] Propylene Carbonate is also permitted for use as a component of adhesives used for food packaging [21CFR175.105]. In addition, according to 40CFR180.950, residues resulting from the use of Propylene Carbonate as either an inert or an active ingredient in a pesticide chemical formulation, including antimicrobial pesticide chemicals, are exempted from the requirement of a tolerance under the Federal Food, Drug, and Cosmetic Act section 408, if such use is in accordance with good agricultural or manufacturing practices.

TOXICOKINETIC STUDIES

Propylene Carbonate did not increase the permeability of evaluated solvents (e.g., benzaldehyde, anisole) in a 4-d assay performed using human abdominal cadaver skin.[4] The permeability rate of Propylene Carbonate was determined to be 0.7 g/m^{2}h in a dermal penetration assay performed using human breast skin samples (compared to be a permeability rate of 24 g/m^{2}h for water). It was concluded that Propylene Carbonate is not readily absorbed through the skin.

Dermal Penetration

In Vitro

The dermal penetration potential of Propylene Carbonate was evaluated in human breast skin samples (thickness of 1-2 mm; 3 total samples).[19] Water [^{3}H] was run through the diffusion cell system for 2 h prior to the test substance to calibrate the relative permeability of samples, and to detect defective specimens. Then, the challenge test was applied to skin samples, and receptor fluid was observed with gas chromatography. Two of the three specimens tested were considered to be defective; however, the normalized permeability constant in the intact specimen was determined to be 0.2 g/m^2 · h.

Absorption, Distribution, Metabolism, and Excretion

In Vitro

The in vitro degradation rate of Propylene Carbonate (1 mmol) in the blood of Wistar rats was evaluated.[6] Ethylene carbonate was used as a control to demonstrate that the hydrolysis of the test item was due to in vitro metabolism, instead of chemical instability. Blood samples (3 samples/group) were incubated with the test substance or controls for 30 min (test substance samples evaluated at 0, 0.5, 1, 5, 10, and 30 min; controls samples evaluated at 0 and 30 min). Approximately 5.5% of the starting concentration of Propylene Carbonate remained after 5 min of incubation. The calculated half-life value of Propylene Carbonate was determined to be 0.734 min (degradation rate of 0.68 µmol/(ml·min)). Nearly complete hydrolysis and stoichiometric formation of propylene glycol was observed after 30 min. The degradation rate of ethylene carbonate was determined to be 0.14 µmol/(ml·min); ethylene glycol was found as a metabolite. In a similar study, Propylene Carbonate (500 µmol) was incubated in blood from Wistar rats (ethylene carbonate used as control; 3 samples/ group). Incubations occurred at 37°C and 4°C for 120 min (evaluations for samples incubated at 37°C at 0, 5, 10 60, and 120 min; evaluations for samples incubated at 4°C at 0 and 120 min). At 37°C, Propylene Carbonate was rapidly degraded and

could not be detected by liquid chromatography with mass spectrometry after 5 min of incubation (hydrolysis likely occurs within a few seconds). Ethylene carbonate was detected at 27% (of administered dose) after 5 min. No Propylene Carbonate or ethylene carbonate were detected after 120 min of incubation at 4°C.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Slight erythema was noted on the abraded skin of albino rabbits (5/sex) treated with 2 mg/kg undiluted Propylene Carbonate (no lesions observed).[2] No signs of dermal toxicity were observed in an acute dermal toxicity assay in which rabbits (n = 6) were exposed to 0.5 ml Propylene Carbonate at shaved skin sites.[4] In other acute dermal toxicity assays performed in rabbits, dermal median lethal doses (LD_{50}) of > 5000 mg/kg (number of animals not stated) and >20 ml/kg (n = 4 males) were established.[2] An acute dermal LD_{50} of >10 ml/kg was established in rabbits (2/sex) treated with an antiperspirant containing 2% Propylene Carbonate. No mortality was observed in an acute dermal toxicity assay in which albino rabbits (2-3/sex/group) were treated with 2000 mg/kg of an underarm stick containing 20% Propylene Carbonate (applied to intact and abraded skin). Gross examination revealed adverse effects in the kidneys of 3 treated animals.

An acute dermal toxicity assay was performed according to Organisation for Economic Co-operation and Development Test Guidelines (OECD TG) 402.[6] Undiluted Propylene Carbonate (2000 mg/kg bw) was applied to the skin of New Zealand white rabbits (5/sex), under occlusive conditions, for 24 h (14-d observation period). The LD_{50} was determined to be > 2000 mg/kg bw. In a similar study performed according to the same procedures, New Zealand white rabbits (5/sex) were administered 3000 mg/kg bw undiluted Propylene Carbonate. The LD_{50} was determined to be > 3000 mg/kg bw.

Oral

An oral LD_{50} of > 5000 mg/kg was determined in an acute oral toxicity study performed in rats (n = 10) given Propylene Carbonate via gavage.[4] In other acute oral toxicity assays performed in mice (number of animals not stated) and rats (5/group) using undiluted Propylene Carbonate, LD_{50}s were determined to be 20,700 and 29,100 mg/kg, respectively (method of oral administration not stated).[2] No adverse effects, aside from one mortality, were observed in an acute oral toxicity assay in which an underarm stick containing 20% Propylene Carbonate was administered to rats (5/sex; method of oral administration not stated)). An acute oral toxicity assay was performed in rats (5/sex) using a cream blush containing 2% Propylene Carbonate (administered as a 25% suspension in corn oil; method of oral administration not stated). Adverse effects observed include poor grooming, soft red stools, and body weight loss in males. An antiperspirant containing 2% Propylene Carbonate was also evaluated for acute oral toxicity in rats (5/sex; administration via gavage). The oral LD_{50} was determined to be > 10 ml/kg. Three lip products containing Propylene Carbonate (2 lip slickers containing 0.54% Propylene Carbonate, each, and a lip gloss containing 0.25% Propylene Carbonate) were evaluated for acute oral toxicity in rats (5/sex; administration via gavage). No toxicity was observed.

Smith-Fischer and Hanover rats were given undiluted Propylene Carbonate in doses of 16 (n = 10/sex), 25 (n = 4/sex), or 29.1 ml/kg (n = 10/sex) via gavage.[6] In the group treated with 29.1 ml/kg, 90 min post-administration, 3 animals died; all animals of this group died within 48 h. Animals that died displayed spotty-reddened lungs, anemic livers, and reddened small intestines. No deaths were reported for animals of the other test groups. The LD_{50} was determined to be 27 ml/kg bw.

Inhalation

Propylene Carbonate was not lethal to 6 rats exposed to concentrated vapors for 8 h.[2] No other details provided.

Rats (6/sex/group; strain not stated) were exposed to Propylene Carbonate vapor (concentration not stated) for 8 h at 20° C and observed for 7 d.[6] No other details were provided for this study. No signs of toxicity were observed.

Subcutaneous

LD_{50} values of 15.8 and 11.1 ml/kg were determined for mice (n = 10 males) and rats (number of animals not stated), respectively, in acute subcutaneous toxicity assays.[2] In these assays, animals were treated with up to 20 ml/kg Propylene Carbonate.

Repeated-Dose Toxicity Studies

No signs of toxicity were observed in a 2-wk toxicity assay in which Propylene Carbonate was dermally applied at a dose of 1000 mg/kg/d.[2] No other details on this study were provided. The dermal toxicity of Propylene Carbonate (3.5, 10.5, and 17.5%) in physiological saline was evaluated in male Wistar rats (number of animals not stated; treatment for 1 mo). A control group was treated with 10% physiological saline. No adverse effects other than hyperkeratosis and an increase in the number of basal cells at treated sites (seen in animals at the two highest test concentrations) were observed. No other signs of toxicity other than rhinorrhea and diarrhea were observed in dogs, guinea pigs, and rats exposed to aerosolized Propylene Carbonate (2.8 mg/l) for 6 h/d, 5 d/wk, for 21 d (no other details provided).

Details on the repeated dose toxicity studies summarized below can be found in Table 3. Statistically significant adverse effects were observed in rats (5/sex/group) treated with Propylene Carbonate (up to 5000 mg/kg bw/d, in deionized

water, via gavage) for 28 d (i.e., increased liver, ovary, and testes weights compared to controls (majority of adverse effects observed with 3000 or 5000 mg/kg bw/d)).[6] A no-observed-adverse-effect-level (NOAEL) of > 5000 mg/kg bw/d was established in an assay in which rats (15/sex/group) were given Propylene Carbonate (in deionized water, via gavage) at doses of up to 5000 mg/kg bw/d for 90 d. Recovery groups treated with the control only or 5000 mg/kg bw/d of the test substance were also evaluated for 28 d following final dose administration. No dose-dependent adverse effects were observed in this study. Toxic effects such as irritation to the eyes, mucous membranes, and nasal cavities were observed in a 9-d inhalation toxicity study performed in rats (5/sex/group) exposed to Propylene Carbonate at up to 5000 mg/m^3 air. A systemic no-observed-adverse-effect-concentration (NOAEC) of 1000 mg/m^3 was determined in a 13-wk inhalation toxicity assay in which rats (15/sex/group) were exposed to aerosolized Propylene Carbonate (6 h exposures/d, 5 d/wk) at concentrations of up to 1000 mg/m^3 air. A local NOAEC of 100 mg/mg^3 air was also established in this assay due to localized signs of toxicity (i.e., periocular swelling (effect also observed in control animals)).

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

A dose range-finding developmental toxicity study was performed in Sprague-Dawley rats (6 females/group) given undiluted Propylene Carbonate (up to 2000 mg/kg bw/d (other doses not stated); via gavage) on gestation days 6-15.[6] Control animals were used in this assay; however, details on control group treatment were not provided. One of the dams in the 2000 mg/kg bw/d group displayed signs of toxicity (e.g., post-dose salivation, piloerection, decreased activity, dyspnea, cyanosis, rales) from gestation days 9 – 13. One dam in the 2000 mg/kg bw/d group was found dead on gestation day 10. No statistically significant differences were observed in treated groups versus controls regarding total number of implantation sites, corpora lutea, viable and non-viable fetuses, early or late resorptions, number of pre- and post-implantation losses, or gross fetal malformations.

A developmental toxicity assay was performed according to OECD TG 414 using Sprague-Dawley rats (27 females/ group).[6] Undiluted Propylene Carbonate (1000, 3000, and 5000 mg/kg/d) was administered to animals, via gavage, on days 6-15 of gestation. Control animals received deionized water only, via gavage. Animals were sacrificed and evaluated on day 20. Decreased maternal body weight gain was observed in dams treated with the highest dose and reduction of food intake was observed in dams treated with the mid and highest dose. The majority of mid- and high-dose animals also exhibited immediate post-dose salivation. Other effects observed include rales, abnormal gait and stance, dyspnea, piloerection, flaccid body tone, nasal discharge, cyanosis, and red discoloration around the mouth. Seven treated animals died during the tested period (2 in mid-dose group and 5 in high-dose group). Necropsy revealed congested, spongy, and discolored lungs, and distended/discolored stomach and intestines. Upon cesarean section, 27, 26, 23, and 22 animals were found gravid in the negative control, low-, mid-, and high-dose groups, respectively. No fetal malformations were observed. A statistically significant reduction in the number of fetuses exhibiting incomplete ossification of the 3rd sternebrae was observed in the low- and mid-dose group when compared to control (this effect was not determined to be of toxicological importance, according to study authors).

GENOTOXICITY STUDIES

An Ames assay was performed testing Propylene Carbonate (50 – 5000 µg/plate) using Salmonella typhimurium strains TA1535, TA1537, TA 1538, TA 98, and TA 100 (with and without metabolic activation).[2] No mutagenicity was observed in most strains; however, minor activity was observed with and without metabolic activation in the TA 100 strain (dose-response relationship not observed). Propylene Carbonate (up to 4000 µg/plate) was negative for genotoxicity in rat hepatocyte primary culture (no other details provided).

In Vitro

An Ames assay was performed in *S. typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100, using Propylene Carbonate (up to 1000 µg/plate; use of vehicle not stated); with and without metabolic activation.[6] The test substance was determined to be non-genotoxic.

In Vivo

A mammalian erythrocyte micronucleus test was performed according to OECD TG 474.[6] CD-1 mice (5/sex/group) received a single intraperitoneal injection of either Propylene Carbonate in distilled water (1666 mg/kg), distilled water (negative control), or triethylenemelamine (positive control).[6] Animals of the test substance group were killed at 30, 48, and 72 h, and bone marrow was evaluated. Propylene Carbonate was non-genotoxic. Controls gave expected results.

CARCINOGENICITY STUDIES

Dermal

The potential carcinogenicity of Propylene Carbonate (50 µl; tested neat) was evaluated in male Jackson C3H/HeJ mice (50/group).[6] A negative control group was left untreated and a positive control group was treated with 0.05% benzo(a)pyrene in acetone. Animals were administered the test substance via the dorsal skin, 2x/wk, for 104 wk (level of occlusion not

stated). No treatment-related skin tumors were observed in the Propylene Carbonate-treated group. A squamous cell carcinoma was observed in the preputial gland duct of a treated mouse; however, this was not considered to be treatment-related based on the site of origin, distance from the treatment site, and lack of evidence of preneoplastic or neoplastic change in the treatment area.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Slight dermal irritation was observed in two assays in which undiluted Propylene Carbonate was applied to the skin of albino rabbits (n = 5 - 6 animals).[2] Five "organically modified clay mastergels," each containing 3% Propylene Carbonate, were evaluated for dermal irritation in New Zealand rabbits (3 males/group). The materials ranged from being slightly irritating to moderately irritating. Similar results were obtained when these mastergels were tested in cumulative skin irritation assays (6-wk) in albino rabbits (6 males/group). A dermal irritation score of 0.2/8.0 (minimally irritating) was determined in a dermal irritation assay performed using rabbits exposed to 0.5 ml Propylene Carbonate to shaved skin sites.[4] All scores returned to normal within 72 h of treatment. Potential dermal irritation was evaluated in rabbits using several products containing Propylene Carbonate at concentrations ranging from 0.51 – 20% (n = 3 - 6).[2] The majority of these products resulted in slight skin irritation; however, moderate irritation was observed in an assay using an antiperspirant containing 2% Propylene Carbonate (6/group (sex not stated)). In studies performed in humans, undiluted Propylene Carbonate resulted in moderate skin irritation (in a study performed in 5 subjects), while 5 - 10% Propylene Carbonate (aqueous solution) produced no irritation or sensitization (n = 50 subjects). Cosmetic products or gels containing 0.54 – 20% Propylene Carbonate were essentially non-sensitizing, and non-irritating to moderately irritating to human skin (n = 26 – 206 subjects).

Details on the dermal irritation and sensitization studies summarized below can be found in Table 4.

Propylene Carbonate (tested neat; no vehicle) was not irritating in a patch test performed in 4 rabbits (occlusive conditions; 20 h patch application).[6] In a clinical study, no significant differences were observed in irritation between the control and the test substance (serum containing 17.84% Propylene Carbonate) in a 24-h single-insult occlusive patch test (SIOPT) performed in 18 subjects.[20] No visible dermal irritation was observed by the evaluating dermatologist in a 5-d (n = 19) or 4-wk (n = 50) use assay in which subjects applied a serum containing 17.84% Propylene Carbonate (applied neat) to the face 1x/d.[21,22] However, perceived discomfort (i.e., burning and stinging) was reported in a few subjects in these studies. A product containing 17.84% Propylene Carbonate (applied neat) was non-sensitizing in a maximization assay performed in 26 subjects.[23]

Phototoxicity/Photosensitization

Products formulated with 1.51 - 20% Propylene Carbonate were generally non-phototoxic and non-photosensitizing (n = 10 – 304 subjects).[2] However, one product containing 20% Propylene Carbonate may have produced a low level photoallergic reaction in 1 of 25 subjects tested (n = 25 subjects).

OCULAR IRRITATION STUDIES

Minimal ocular irritation was observed when undiluted Propylene Carbonate was administered to rabbit eyes (n = 3 rabbits).[2] In another study, yellow ocular discharge was noted in rabbits (3/group (sex not stated)) treated with undiluted Propylene Carbonate; however, no irritation was observed in the same study at lower treatment concentrations (up to 17.5%). Moderate irritation was observed in two assays in which Propylene Carbonate (concentration not stated) was administered into the eyes of rabbits (number of animals not stated). Five "organically-modified clay mastergels" containing 3% Propylene Carbonate were evaluated for ocular irritation in rabbits (n = 6 male rabbits). Test materials ranged from slightly irritating to irritating. Cosmetic products containing Propylene Carbonate (a blush cream containing 2% Propylene Carbonate and two lip products containing 0.54% Propylene Carbonate, were tested for ocular irritation in 8 different studies (all studies performed in rabbits (6 rabbits/product (sex not stated)). The majority of the studies resulted in no irritation or minimal irritation. In studies in which irritation (slightly irritating to irritating) was observed, effects were reversible. An ocular irritation score of 12.5/110 (minimally irritating) was determined 1-h post treatment in an ocular irritation assay performed in rabbit eyes (n = 6 rabbits (sex not stated)) exposed to 0.1 ml Propylene Carbonate.[4] Slight ocular irritation was observed through 72 h; however, all scores returned to normal by day 7 post-treatment.

Details regarding the ocular irritation studies summarized below can be found in Table 5.

A mean stain-retention score of 1.8 ± 1.5 on day 1 of treatment was observed in a porcine corneal opacity reversibility assay in which excised porcine eyes were exposed to a hair glazing product containing 15 – 25% Propylene Carbonate.[24] The mean stain-retention scores on day 1 of treatment for phosphate-buffered saline (PBS; negative control), ethanol (positive control), and sodium hydroxide (positive control) were 0.9 ± 1, 1.5 ± 0.6, and 3.0 ± 0.8, respectively. An EC_{90} (estimated concentration of what causes effects indicative of serious eye damage within 90 s) of 17% was determined in a hen's egg chorioallantoic membrane (HET-CAM) assay in which eggs were incubated with 10 – 100% Propylene Carbonate in distilled water.[6] Slight edema and cloudiness were observed 1 h after administration of Propylene Carbonate (tested neat; no vehicle) into the eyes of 3 rabbits (sex not stated). In another study using 3 rabbits, Propylene Carbonate (tested neat; no vehicle) was

determined to be moderately irritating in an ocular irritation assay. Conversely, Propylene Carbonate (tested neat; no vehicle) was considered to be non-irritating in an ocular irritation assay performed in 6 rabbits (sex not stated).

SUMMARY

Propylene Carbonate is reported to function in cosmetics as a solvent and viscosity-decreasing agent. Propylene Carbonate was previously reviewed by the Panel in a safety assessment published in 1987. At that time, the Panel concluded that Propylene Carbonate is safe in the present practices of use and concentration described in that report. This conclusion was reconsidered at the September 2004 Panel meeting and re-affirmed, as published in 2006. In 2023, the Panel determined that this safety assessment should be opened for re-evaluation due to an increase in frequency and concentration of use.

RLD submitted in 2024 indicate that Propylene Carbonate is used in 13,340 total formulations. According to 2023 VCRP survey data, Propylene Carbonate was reported to be used in 882 total formulations. The results of the concentration of use survey conducted by the Council in 2022 indicate that this ingredient is used at up to 17.9% in leave-on formulations. In 2002/2003, this ingredient was reported to be used in 178 formulations, at up to 5%.

The permeability constant of Propylene Carbonate was determined to be 0.2 $g/m^2 \cdot h$ in a dermal penetration assay performed using human breast skin samples (this value was for 1/3 tested samples; 2 of the tested samples were defective). The half-life value of Propylene Carbonate was determined to be 0.734 min in an assay evaluating the degradation rate of Propylene Carbonate in rat blood. In a different in vitro degradation assay using rat blood, Propylene Carbonate was rapidly degraded and could not be detected after 5 min of incubation.

LD_{50}s of ≥ 2000 mg/kg bw and ≥ 3000 mg/kg bw were determined in 2 acute dermal toxicity assays performed in rabbits exposed to undiluted Propylene Carbonate under occlusive conditions. An LD_{50} of 27 ml/kg bw was determined in an acute oral toxicity assay performed using rats given 16 or 29.1 ml/kg undiluted Propylene Carbonate via gavage. No signs of toxicity were observed in an acute inhalation assay in which rats were exposed to Propylene Carbonate vapor for 8 h.

Adverse effects such as increased organ weights were observed in a 28-d assay in which rats were given Propylene Carbonate (up to 5000 mg/kg bw/d) via gavage. An NOAEL of > 5000 mg/kg bw/d was established in an assay in which rats were given Propylene Carbonate via gavage at doses of up to 5000 mg/kg bw/d. Toxic effects such as irritation to the eyes, mucous membranes, and nasal cavities were observed in a 9-d inhalation toxicity performed in rats exposed to Propylene Carbonate at up to 5000 mg/m^3 air. A systemic NOAEC of 1000 mg/m^3 was determined in a 13-wk inhalation toxicity assay in which rats were exposed to aerosolized Propylene Carbonate (6 h exposures/d, 5 d/wk) at concentrations of up to 1000 mg/m^3 air. The local NOAEC was determined to be 100 mg/m^3 air.

No adverse effects regarding developmental and reproductive parameters evaluated (e.g., total number of implantation sites, gross fetal malformations) were observed in an assay performed using rats given undiluted Propylene Carbonate (up to 2000 mg/kg bw/d) via gavage on gestation days 6 – 15. However, one high-dose dam exhibited signs of toxicity (e.g., cyanosis) and one high-dose dam was found dead on gestation day 10. Adverse effects (e.g., rales, dyspnea, cyanosis, death) were observed in maternal animals in mid- and high-dose animals in a developmental toxicity assay performed in rats (undiluted Propylene Carbonate administered via gavage at 1000, 3000, and 5000 mg/kg/d via gavage on gestation days 6 - 15). No fetal malformations were observed in this assay; however, a statistically significant reduction in the number of fetuses exhibiting incomplete ossification of the 3rd sternebrae was observed in the low- and mid-dose group when compared to control (this effect was not determined to be of toxicological importance, according to study authors).

Propylene Carbonate (up to 1000 µg/plate) was not considered to be genotoxic in an Ames assay performed using *S. typhimurium* strains with and without metabolic activation. Similarly, no genotoxicity was observed in a mammalian erythrocyte micronucleus assay in which mice were given a single intraperitoneal injection of Propylene Carbonate (1666 mg/kg) in distilled water.

No treatment-area skin tumors were observed in a dermal carcinogenicity assay performed using mice exposed to undiluted Propylene Carbonate (50 µl). Applications occurred 2x/wk for 104 wk.

No irritation was observed in a dermal irritation assay performed using rabbits exposed to Propylene Carbonate (tested neat) for 20 h under occlusive conditions. In a clinical study, no significant differences were observed in irritation between the control and the test substance (serum containing 17.84% Propylene Carbonate) in a human 24-h SIOPT. No visible dermal irritation was observed by the evaluating dermatologist in a 5-d or 4-wk use assay in which subjects applied a serum containing 17.84% Propylene Carbonate (applied neat) to the face 1x/d. A product containing 17.84% Propylene Carbonate (applied neat) was non-sensitizing in a maximization assay.

A mean stain-retention score of 1.8 ± 1.5 on day 1 of treatment was observed in a porcine corneal opacity reversibility assay in which excised porcine eyes were exposed to a hair glazing product containing 15 – 25% Propylene Carbonate (mean retention score of negative control was 0.9 ± 1). An EC_{90} of 17% was determined in a HET-CAM assay in which eggs were incubated with 10 – 100% Propylene Carbonate in distilled water. Slight edema and cloudiness were observed 1 h after administration of Propylene Carbonate (tested neat; no vehicle) into the eyes of 3 rabbits (sex not stated). In another study using 3 rabbits, Propylene Carbonate (tested neat) was determined to be moderately irritating in an ocular irritation assay

using rabbits. Conversely, undiluted Propylene Carbonate was considered to be non-irritating in a different ocular irritation assay performed in 6 rabbits.

DISCUSSION

In accordance with its Procedures, the Panel re-evaluates the conclusion of previously-issued reports approximately every 15 years. In 1987, the Panel published a final report on Propylene Carbonate and concluded that this ingredient was safe as used as a cosmetic ingredient in the present practices of use and concentration, as stated in that report. This conclusion was re-affirmed in a re-review published in 2006. The Panel again considered a re-review of this ingredient at the March 2023 meeting and re-opened the report due to increased frequency and concentration of use. After review of the previous and new data, the Panel issued a revised conclusion stating Propylene Carbonate is safe in cosmetics in the present practices of use and concentration, as described in this safety assessment, when formulated to be non-irritating. The Panel was concerned that the potential exists for dermal irritation due to reports of sensory irritation.

In addition, the Panel noted that this ingredient is used in baby products, but concentrations of use were not reported for this product category. However, the primary concern was potential irritation, and the Panel's caveat stating that products containing this ingredient are to be formulated to be non-irritating mitigates this concern.

The Panel also noted the photoallergic reaction observed in 1 out of 25 subjects in a dermal photosensitization assay using 20% Propylene Carbonate. However, this ingredient is transparent in the UV region and lacks a chromophore functional group, thereby mitigating any concern for its potential to induce phototoxicity or photosensitization.

The Panel reviewed the available inhalation toxicity data and discussed the issue of incidental inhalation exposure resulting from this ingredient; for example, Propylene Carbonate is reported to be used in face powders and deodorant sprays at up to 1.4% and could be possibly inhaled. The Panel noted that the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient. Coupled with the small actual exposure in the breathing zone, high systemic (1000 mg/m^3) and local (100 mg/m^3) NOAECs in a 13-wk inhalation performed in rats (exposure 5 d/wk, 6 h/d), 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.

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

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Propylene Carbonate is safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

TABLES

Table 1. Chemical properties

Property	Value	Reference
Physical Form	liquid	2
Color	colorless	2
Odor	odorless	2
Molecular Weight (g/mol)	102.09	2
Density (g/ml @ 20ºC)	1.2609	2
Viscosity (cp @ 20ºC)	2.76	2
Vapor pressure (mmHg@ 20ºC)	0.03	2
Melting Point (ºC)	-49	6
Boiling Point (ºC)	241.6	8
Water Solubility (g/l @ 25ºC & pH 7)	200	6
log K_{ow} (@ 20ºC)	-0.41 (estimated)	6
Disassociation constants (pKa @ 20ºC)	3.92	6

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

	# of Uses			Max Conc of Use	
	RLD (2024)[14]	VCRP (2023)[15]	VCRP (2002)[3]	% (2022)[16]	% (2003)[3]
Totals*	**13, 340**	**882**	**178**	**0.0064 -17.9**	**0.003 - 5**
summarized by likely duration and exposure**					
Duration of Use					
Leave-On	***	*874*	*139*	*0.0064 – 17.9*	*0.003 – 5*
Rinse-Off	***	*8*	*38*	*0.24 – 6*	*0.1 – 2*
Diluted for (Bath) Use	***	*NR*	*1*	*NR*	*NR*
Exposure Type					
Eye Area	***	204	68	0.01 – 2.7	0.2 - 4
Incidental Ingestion	***	389	35	0.0064 – 3.9	0.03 – 2
Incidental Inhalation-Spray	***	29[a]; 13[b]	7[a]	0.28	0.02 – 0.2[a]
Incidental Inhalation-Powder	***	7; 13[b]; 13[c]	NR	1.4; 0.05 – 6[c]	0.4
Dermal Contact	***	442	113	0.01 – 17.9	0.02 – 5
Deodorant (underarm)	***	33[a]	2[a]	0.93 – 1.4	0.2 – 5[a]
Hair - Non-Coloring	***	3	1	0.24	NR
Hair-Coloring	***	2	1	NR	NR
Nail	***	5	6	0.15 – 6	0.003 – 4
Mucous Membrane	***	389	62	0.0064 – 3.9	0.03 – 2
Baby Products	***	3	NR	NR	NR
as reported by product category					
Baby Products	***4***				
Baby Shampoos	3	NR	NR	NR	NR
Baby Lotions/Oils/Powders/Creams		2	NR	NR	NR
Other Baby Products	1 (l.o.)	1	NR	NR	NR
Bath Preparations	***1***				
Bath Oils, Tablets, and Salts	NR	NR	1	NR	NR
Bubble Baths	1	NR	NR	NR	NR
Eye Makeup Preparations (other than children's eye makeup preparations)	***2579***				
Eyebrow Pencil	258	15	6	0.08 – 0.36	0.3
Eyeliner	707	58	15	0.14 – 2.7	0.2 – 0.6
Eye Shadow	922	47	10	0.01 – 0.7	0.4 – 1
Eye Lotion	20	3	NR	NR	NR
Eye Makeup Remover	15	4	3	NR	NR
False Eyelashes	1	NA	NR	NR	NR
Mascara	360	44	22	0.75 – 2.2	2 – 4
Eyelash and Eyebrow Adhesives, Glues, and Sealants	35	NA	NR	NR	NR
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	104	NA	NR	NR	NR
Eyelash Cleansers	19	NA	NR	NR	NR
Other Eye Makeup Preparations	306	33	12	0.34	0.5
Hair Preparations (non-coloring)	***87***				
Hair Conditioners	2 (l.o.); 2 (r.o.)	NR	NR	NR	NR
Hair Sprays (aerosol fixatives)	8	NR	NR	NR	NR
Rinses (non-coloring)	1	NR	NR	NR	NR
Shampoos (non-coloring)	7 (l.o.); 52 (r.o.)	NR	NR	0.24	NR
Tonics, Dressings, and Other Hair Grooming Aids	6	1	1	NR	NR
Other Hair Preparations	4 (l.o.); 6 (r.o.)	1	NR	NR	NR
Hair Coloring Preparations	***96***				
Hair Dyes and Colors (all types requiring caution statements and patch tests)	10	NR	NR	NR	NR
Hair Tints	44	NR	NR	NR	NR
Hair Rinses (coloring)	1 (r.o.)	NR	NR	NR	NR
Hair Color Sprays (aerosol)	14	NR	NR	NR	NR
Hair Bleaches	4	NR	NR	NR	NR
Eyelash and Eyebrow Dyes	6	NA	NR	NR	NR
Other Hair Coloring Preparation	17 (l.o.); 1 (r.o.)	NR	1	NR	NR
Makeup Preparations (not eye; not children's)	***9424***				
Blushers and Rouges (all types)	602	17	1	0.04 – 0.76	0.1 – 2
Face Powders	37	7	NR	1.4	0.4
Foundations	2978 (traditional application); 111 (airbrush application)	60	3	0.16 – 0.45	0.6 – 2
Leg and Body Paints	16 (traditional application)	2	NR	NR	NR
Lipsticks and Lip Glosses	4848	389	35	0.0064 – 3.9	0.03 - 2
Makeup Bases	127 (traditional application)	21	4	0.03 – 0.075	NR

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

	# of Uses			Max Conc of Use	
	RLD (2024)[14]	**VCRP (2023)[15]**	**VCRP (2002)[3]**	**% (2022)[16]**	**% (2003)[3]**
Makeup Fixatives	71	1	2	NR	NR
Other Makeup Preparations	994 (l.o.); 28 (r.o.)	65	20	0.16 – 0.84	1
Makeup Preparations for Children (not eye)	***15***				
Children's Blushers and Rouges (All Types)	4	NA	NR	NR	NR
Children's Lipsticks and Lip Glosses	11	NA	NR	NR	NR
Manicuring Preparations	***665***				
Basecoats and Undercoats	11	2	NR	NR	NR
Cuticle Softeners	2	NR	NR	0.6	NR
Nail Creams and Lotions	1	NR	NR	0.15	NR
Nail Polishes and Enamels	553	1	NR	1.1	0.003
Nail Polish and Enamel Removers	107	NR	6	6	1
Other Manicuring Preparations	5	2	NR	NR	4
Oral Products	***1***				
Other Oral Products	1	NR	NR	NR	NR
Personal Cleanliness	***148***				
Bath Soaps and Body Washes	57	NR	NR	NR	NR
Deodorants (underarm)	3 (not spray); 8 (aerosol)	33	2	0.93 – 1.4 (aerosol)	0.2 – 5
Disposable Wipes	6	NA			
Other Personal Cleanliness Products	62 (l.o.); 12 (r.o.)	NR	26	NR	NR
Skin Care Preparations (creams, lotions, powder, and sprays)	***442***				
Cleansing (cold creams, cleansing lotions, liquids, and pads)	11	4	1	0.78 – 1.7	0.1
Face and Neck (excluding shaving preparations)	277 (l.o.); 19 (r.o.)	11	NR	3.8–6 (not spray)	NR
Body and Hand (excluding shaving preparations)	23 (l.o.); 5 (r.o.)	13	NR	0.05 (not spray)	NR
Foot Powders and Sprays	3	NR	NR	0.28	NR
Moisturizing	158	22	4	0.45 (not spray)	0.02 – 0.2
Night	7	4	1	17.9 (not spray)	NR
Paste Masks (mud packs)	4	NR	1	NR	0.3 - 2
Skin Fresheners	1	1	NR	NR	NR
Other Skin Care Preparations	48 (l.o.); 15 (r.o.)	17	NR	NR	NR
Suntan Preparations	***39***				
Suntan Gels, Creams, and Liquids	33	1	1	0.02–0.2 (not spray)	0.08 – 0.2
Indoor Tanning Preparations	4 (traditional application); 1 (spray application)	NR	NR	NR	NR
Other Suntan Preparations	2	NR	NR	NR	NR
Tattoo Preparations	***1***				
Temporary Tattoo Inks	1	NA	NR	NR	NR
Other Preparations (i.e., those preparations that do not fit another category)	***91***				

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

Table 3. Repeated dose toxicity studies[6]

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results
ORAL						
Propylene Carbonate	Deionized water	Sprague-Dawley rats (5/sex/group)	28 d	0, 500, 1000, 2000, 3000, and 5000 mg/kg bw/d	OECD TG 407; treatment 5 d/wk; gavage administration	Post-dose salivation observed in some animals of all test doses. One male treated with 5000 mg/kg bw/d exhibited alopecia and scab formation on day 11-28. One female treated with 5000 mg/kg bw/d displayed decreased activity and lacrimation on day 9, another 5000 mg/kg bw/d-treated female displayed decreased activity on days 14-17. A statistically significant, dose-dependent increase in absolute ovary weights in females treated with 3000 and 5000 mg/kg bw/d was observed, compared to controls. Statistically significant increased relative liver weights were also observed in females treated with 1000 and 5000 mg/kg bw/d (compared to controls). Males treated with 5000 mg/kg bw/d displayed a statistically significant increase in testes weight (compared to controls). One female in the 3000 mg/kg bw/d group had a small left adrenal gland (50% smaller than right); one female from 5000 mg/kg bw/d group had hollow pelves of the left and right kidneys.
Propylene Carbonate	Deionized water	Sprague-Dawley rats (15/sex/group)	90 d	0, 1000, 3000, and 5000 mg/kg bw/d	OECD TG 408; treatment 5 d/wk; gavage administration; additional control and high dose groups served as recovery groups observed for 28 d after final dose administration; interim necropsies performed (day 30, day 90, or terminal necropsy (day 118))	Adverse effects that were observed at all dose levels include immediate post-dose salivation, rales, abnormal gait, abnormal stance, decreased activity, and dyspnea. Adverse effects observed at the mid-dose level include chromodacryorrhea, dislodged upper incisors, and increased blood phosphorous values (in males). Five high dose rats died during the study and 5 treated rats in recovery group died during test article administration (deaths were not considered to be test article related). A significant reduction of mean body weight, body weight gain, and food consumption observed in high-dose recovery males compared to recovery controls. A significant decrease in corpuscular volume was observed in high-dose males (compared to controls); significant increases in red blood cell counts, hematocrit, and hemoglobin observed in high-dose females (compared to controls). Clinical chemistry abnormalities observed include increased bilirubin, albumin, creatinine, chloride; decreased phosphorus, glucose, protein, calcium (effects observed predominantly in high- and/or mid-dose groups). Effects observed in the low-dose group include significant increases in bilirubin and phosphorous (in females) and statistically significant decrease in glucose (both sexes). A statistically significant increase in high-dose male absolute brain weight was observed at the 30-d interim necropsy; no significant differences were noted for the female absolute organ weights at day 30 or male and female organ weights at day 90. At the day 118 necropsy, significantly reduced kidney weights were observed in high-dose males (effect not observed in females). Several gross pathological observations were observed (e.g., enlarged cervical lymph nodes, submandibular mass, mottled and pitted kidneys); however, these effects were non-specific, low in incidence, and not dose-dependent. No test-article related lesions were present in any of the tissues evaluated upon histopathological evaluation. The degree of spermatogenesis of the testes of the high dose males and the ovarian activity of the high dose females were similar to control animals. Per the report, an NOAEL > 5000 mg/kg bw/d was determined.

Table 3. Repeated dose toxicity studies[6]

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results
INHALATION						
Propylene Carbonate	No vehicle	Fischer 344 rats (5/sex/group)	9 d	0, 1000, 2500, and 5000 mg/m^3 air	OECD TG 412; whole-body exposure to aerosolized test substance; 6h exposures, 5 d/wk	All animals exposed to the highest dose and all females and 3 males exposed to 2500 mg/m^3 were observed to be unkept at least once during the study (due to lack of grooming or inability to groom test substance from fur). At the highest tested dose, ocular and respiratory tract irritation (i.e., reddened eyes, swollen periocular tissue, perinasal encrustation) as well as uriogenital wetness, ataxia, and emaciation were observed. Females exposed to 2500 mg/m^3 also displayed ocular irritation, respiratory irritation, urogenital wetness. Urogenital wetness was also observed in female animals exposed to the lowest tested dose. The majority of these effects, excluding ocular irritation, were considered to be transient as they were not present during the second week of exposures. A statistically significant decrease in male and female body weight gain was observed at all exposure concentrations (compared to controls). Absolute and relative liver weights along with relative kidney weights were statistically significantly increased in female animals of the high-dose group. Squamous metaplasia of the maxillary and/or nasal turbinates was observed in 2 females of the high dose-group (this effect was also observed in 2 animals of the control group), and respiratory epithelial necrosis was observed in 1 female of the high-dose group. Significant histologic changes of the larynx and eye (bilateral keratitis, unilateral superficial corneal ulcer, squamous metaplasia of the arytenoid cartilages) were observed in 1 male rat of the high-dose group. No mortality was observed.
Propylene Carbonate	No vehicle	Fischer 344 rats (15/sex/group)	13 wk	0, 100, 500, and 1000 mg/m^3 air	OECD TG 413; whole-body exposure to aerosolized test substance; 6-h exposures, 5 d/wk	Periocular swelling was observed in 13 – 33% of male animals in the test substance-exposed groups. Female animals were also observed to have periocular swelling; however, this effect was also observed at a high frequency in the control group. In addition, this effect was the only treatment-related effect observed in this assay. A systemic NOAEC of 1000 mg/m^3 air, a local LOAEC of 500 mg/m^3 air, and a local NOAEC of 100 mg/mg^2 air were determined.

LOAEC = lowest-observed-adverse-effect-concentration; NOAEC: no-observed-adverse-effect-concentration; OECD = Organisation of Economic Co-operation and Development TG = test guideline

Table 4. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Protocol	Results	Reference
IRRITATION						
ANIMAL						
Propylene Carbonate	No vehicle	0.5 g; 100%	4 Vienna white rabbits (sex not specified)	Test substance applied to shaved skin under occlusive conditions for 20 h; application area: 2.5 cm x 2.5 cm; observations at 1, 5, 15 min, and 20 h after treatment	Non-irritating	6
HUMAN						
Serum containing 17.84% Propylene Carbonate	No vehicle	100%	18 subjects	24-h SIOPT; reference control used (details regarding control treatment not provided)	Primary irritation index of test substance: 0.06/4; 2 ± reactions were observed Primary irritation index of control: 0.00/4 No significant difference between test material and reference control.	20

Table 4. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Protocol	Results	Reference
Serum containing 17.84% Propylene Carbonate	No vehicle	1 ml; 100%	19 subjects	Test substance applied to both sides of the face 1x/d for 5 d; reference control used (details regarding control treatment not provided)	Four subjects reported discomfort during the study (burning and stinging; ranging from mild to severe); 2 subjects also reported discomfort with use of the control The majority of users described products as either very or somewhat gentle; the 4 individuals who experienced discomfort rated the product as somewhat or very irritating The evaluating dermatologist did not observe any visible clinical irritation throughout the study.	[21]
Serum containing 17.84% Propylene Carbonate	No vehicle	3 – 4 drops; 100%	50 subjects	4-wk clinical use assay; once daily application to entire face, including undereye and crow's feet areas	Three subjects reported experiencing episodic discomfort (i.e., burning) during the study period. These episodes were reported to be transient and mild in intensity. One subject reported eye burning; however, this effect did not occur when the subject applied the product a short distance from the eyelid margins. The evaluating dermatologist did not observe any product-related irritation. According to the researchers, the test substance yielded acceptable results.	[22]
SENSITIZATION						
HUMAN						
Product containing 17.84% Propylene Carbonate	No vehicle	0.05 ml; 100%	26 subjects	Maximization assay Induction phase: 0.25% sodium lauryl sulfate applied under occlusive conditions for 24 h; after 24 h, patch removed and test substance applied under occlusive conditions for 48 – 72 h; if no irritation was present, a 0.25% sodium lauryl sulfate patch was again reapplied to the same site for 24 h. followed by reapplication of a fresh induction patch with the test material; this process was repeated for a total of 5 induction exposures Challenge phase: after a 10-d rest period, virgin sites were pre-treated with occlusive patches of 0.25% sodium lauryl sulfate for 1 h, followed by application of the test substance under occlusive conditions for 48 h; sites were graded 15-30 min and 24, 48, and 72 h after patch removal	Non-sensitizing	[23]

SIOPT = single-insult occlusive patch test

Table 5. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
IN VITRO						
Hair glazing product containing 15 - 25% Propylene Carbonate, 1 -5% citric acid, and 5 - 10% ethanol (remaining constituents not stated)	No vehicle	10 µl; 100%	4-8 samples/group	Porcine corneal opacity reversibility assay; corneas of excised porcine eyes treated with test substance or controls (PBS as negative control; ethanol used as positive control with reversible effects; sodium hydroxide as positive control with irreversible effects;) for 5 min, then rinsed with PBS; corneas evaluated via fluorescein staining; evaluations on days 1, 2, 3, 7, 10, 14, and 21	Test substance results: mean stain-retention score: 1.8 ± 1.5 on day 1 and decreased to 0.4 ± 0.7 on day three; no stain retention by day 7; decreased cellularity of superficial squamous cell layer observed in corneas (reversible damage); no effects on any other layer of cornea Negative control (PBS) results: mean stain-retention score: 0.9 ± 1.5 on day 1; all corneas showed loss of stain retention by day 3; no histological abnormalities Positive control (ethanol) results: mean stain-retention of 1.5 ± 0.6 on day 1; showed complete loss of stain by study day 2 or 3; histological effects not stated in report Positive control (sodium hydroxide): mean stain-retention score of 3.0 ± 0.8 on day 1; retained stain for 14 d; microscopic changes to epithelium and stroma; decreased cellularity, necrosis and sloughing on several corneal layers; thickened stroma	[24]
Propylene Carbonate	Distilled water	0.3 ml; 10, 20, 40, 60, 80, and 100%	1-4 samples/group	HET-CAM assay; eggs incubated with test substance; positive control: aqueous solution of NaOH and sodium dodecyl sulfate; EC_{90} evaluated	Predicted category 1 irritant based on GHS criteria (irreversible effects on the eye; threshold concentration for effects indicating serious eye damage; >10% <20%); EC_{90} = 17%; results of positive control not stated	[6]
ANIMAL						
Propylene Carbonate	No vehicle	1 drop; 100%	3 Vienna rabbits (sex not stated)	Test substance applied to right eye; left eye treated with saline (control); 8-d observation period	Test substance resulted in light edema and cloudiness observed 1 h after administration; slight cloudiness observed 8 d after administration (control results not provided)	[6]
Propylene Carbonate	No vehicle	0.1 ml; 100%	3 male New Zealand white rabbits	OECD TG 405; 10-d observation period; control left untreated	Moderately irritating; class 5 on a 1 - 8 scale; effects fully reversible within 10 d; control results not provided	[6]
Propylene Carbonate	No vehicle	0.1 ml; 100%	6 New Zealand White rabbits (sex not stated)	OECD TG 405; 7-d observation period; control left untreated	Maximum mean total scores at 1 h: 12.5/110 24 h: 9.8/110 48 h: 5.1/110 72 h: 4.8/110 7 d: 0/100 test substance considered non-irritating according to CLP Regulation (EC) 1272/2008; control results not provided	[6]

CLP = classification, labeling, and packaging; EC = European Commission; EC_{90} = estimated concentration of what causes effects indicative of serious eye damage within 90 s; GHS = globally harmonized system; HET-CAM = hen's egg chorioallantoic membrane; OECD = Organisation of Economic Co-operation and Development; PBS = phosphate-buffered saline; TG = test guideline

REFERENCES

1. Nikitakis J, Kowcz A. 2024. *wINCI: International Cosmetic Ingredient Dictionary and Handbook*. https://incipedia.personalcarecouncil.org/winci/ Last Updated: 2024. Date Accessed: May 15, 2024.
2. Andersen FA (ed). Final Report on the Safety Assessment of Propylene Carbonate. *J Am Coll Toxicol*. 1987;6(1):23–51.
3. Andersen FA (ed). Annual review of cosmetic ingredient safety assessments - 2004/2005. *IJT*. 2006;25:55–57.
4. Benes D. 2004. Propylene Carbonate: new data for consideration of re-review. [Unpublished report submitted to the Expert Panel for Cosmetic Ingredient Safety for review at the September 9-10, 2004 Washington, DC meeting: Available upon request from CIR].
5. Fiume MM, Bergfeld WF, Belsito DV, et al. Safety assessment of propylene glycol, tripropylene glycol, and PPGs as used in cosmetics. *Int J Toxicol*. 2012;31(5 Suppl):245S–60S. https://pubmed.ncbi.nlm.nih.gov/23064775/. Accessed Mar 19, 2025.
6. European Chemicals Agency. 2024. Propylene Carbonate. https://echa.europa.eu/es/registration-dossier/-/registered-dossier/16088 Last Updated: 2024. Date Accessed: May 16, 2024.
7. Forero JB, Munoz JH, Jones J, da Silva FM. Propylene carbonate in organic synthesis: exploring its potential as a green solvent. *Curr Org Synth*. 2016;13:834–846.
8. PubChem. 2024. Propylene Carbonate. https://pubchem.ncbi.nlm.nih.gov/compound/Propylene-carbonate#section=Boiling-Point Last Updated: 2024. Date Accessed: August 5, 2024.
9. Kotyrba Ł, Chrobok A, Siewniak A. Synthesis of Propylene Carbonate by Urea Alcoholysis—Recent Advances. *Catalysts*. 2022;12(3).
10. Louisiana State University Macromolecular Studies Group. 2025. UV Cutoff. https://macro.lsu.edu/HowTo/solvents/UV%20Cutoff.htm Last Updated: 2025. Date Accessed: March 19, 2025.
11. Ulbrich W, Lamprecht A. Fluorimetric quantification of clodronate and alendronate in aqueous samples and in serum. *Talanta*. 2011;84(2):437–442.
12. Fujinaga T, Izutsu K. Propylene carbonate: purification and tests for purity. *Pure and Applied Chemistry*. 1971;27(1-2):273–280. Accessed Mar 19, 2025.
13. United States Food and Drug Administration. Federal Food, Drug, and Cosmetic Act Section 612 Title 21.
14. US Food and Drug Administration Office of the Chief Scientist. 2024. Registration and Listing Data - Frequency of Use of Cosmetic Products. College Park, MD [Obtained under the Freedom of Information Act from the Division of Freedom of Information; requested as "Frequency of Use Data" July 17, 2024; received July 30, 2024].
15. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2023. Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD [Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2023; received February 2, 2023].
16. Personal Care Products Council. 2023. Concentration of use by FDA product category: Propylene Carbonate. [Unpublished data submitted by Personal Care Products Council on July 5, 2023].
17. EUR-Lex. 2024. Access to European Union Law. https://eur-lex.europa.eu/homepage.html Last Updated: 2024. Date Accessed: July 3, 2024.
18. US Food and Drug Administration. 2024. Inactive Ingredient Search for Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm Last Updated: 2024. Date Accessed: August 5, 2024.
19. Ursin C, Hansen CM, Van Dyk JW, Jensen PO, Christensen IJ, Ebbehoej J. Permeability of commercial solvents through living human skin. *Am Ind Hyg Assoc J*. 1995;56(7):651–660.
20. Anonymous. 2004. Clinical evaluation report: human patch test (serum containing 17.84% Propylene Carbonate). [Unpublished data submitted by Personal Care Products Council on March 13, 2023].
21. Anonymous. 2004. Five-day facial use test (serum containing 17.84% Propylene Carbonate). [Unpublished data submitted by Personal Care Products Council on March 13, 2023].
22. Anonymous. 2004. Clinical use test (serum containing 17.84% Propylene Carbonate). [Unpublished data submitted by Personal Care Products Council on March 13, 2023].
23. Anonymous. 2004. An evaluation of the contact-sensitization potential of a topical coded product in human skins by means of a maximization assay (product containing 17.84% Propylene Carbonate). [Unpublished data submitted by Personal Care Products Council on May 30, 2023].

24. Donahue DA, Avalos J, Kaufman LE, Simion FA, Cerven DR. Ocular irritation reversibility assessment for personal care products using a porcine corneal culture assay. *Toxicol In Vitro*. 2011;25(3):708–714.

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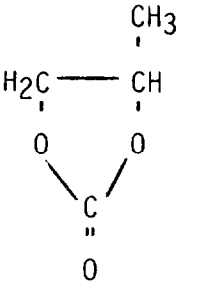
Final Report on the Safety Assessment of Propylene Carbonate

Propylene Carbonate is a nonviscous, clear liquid that is used in cosmetic products at concentrations ranging from ≤0.1% to 5%. Undiluted Propylene Carbonate produced minimal to moderate ocular irritation and slight erythema in rabbits. The dermal LD_{50} in rabbits of the undiluted ingredient was >20 ml/kg. Undiluted Propylene Carbonate was nontoxic by inhalation to dogs and guinea pigs in a 21-day study. Propylene Carbonate was negative for mutagenicity in the Ames Assay, and negative for genotoxicity in the Rat Hepatocyte Primary Culture/DNA Repair Test. In clinical studies, undiluted Propylene Carbonate caused moderate skin irritation, whereas 5 and 10% Propylene Carbonate in aqueous solution produced no skin irritation or sensitization. Cosmetic products containing up to 20% Propylene Carbonate were essentially nonsensitizing and, at most, moderately irritating to human skin, nonphototoxic, and nonphotosensitizing. It is concluded that Propylene Carbonate is safe as a cosmetic ingredient in the present practices of use and concentration.

CHEMISTRY

Propylene Carbonate (CAS Number: 108-32-7) is the organic compound that conforms to the formula[1]:



Other names for Propylene Carbonate include the following: 4-methyl-1,3-dioxolan-2-one; 4-methyldioxalone-2; dipropylene carbonate; 1,2-propanediol-carbonate; 1,2-PDC; cyclic methylethylene carbonate; cyclic propylene carbo-

nate; cyclic 1,2-propylene carbonate; 1,2-propanediol cyclic carbonate; 1,2-propanediyl carbonate; 1,2-propylene carbonate; propylene glycol cyclic carbonate; 4-methyl-2-oxo-1,3-dioxolane; 1-methylethylene carbonate; carbonic acid, cyclic propylene ester; and carbonic acid, cyclic methylethylene ester.[1-7]

In cosmetic products, Propylene Carbonate functions as a polar solvent (or polar additive). Polar solvents have high dielectric constants, are chemically active, and form coordinate covalent bonds.[3,8-11]

Propylene Carbonate is an odorless, nonviscous, clear liquid. It is miscible with methanol, ethanol, acetone, benzene, chloroform, ether, ethyl acetate, cellulose resins, bisphenol resins, and various polymeric materials and immiscible with carbon tetrachloride, hexane, and heptane. Propylene Carbonate is only partially soluble (8.3%) in water. However, aqueous solutions can be readily saturated with this material. The solubility of Propylene Carbonate in water is increased by the presence of perchlorate iron. The compound is nonhygroscopic, noncorrosive, and nonexplosive and does not undergo polymerization. It has little tendency to form emulsions and can react with oxidizing materials. Hydrolysis occurs with boiling of the aqueous solution, whereas thermal decomposition occurs at temperatures above 200°C. If an acid, base, or salt is present in the aqueous solution of Propylene Carbonate, decomposition will occur.* Primary decomposition products of Propylene Carbonate to these materials include propylene glycol, propylene oxide,† propionaldehyde, allyl alcohol, and carbon dioxide. The rate of decomposition increases with increasing temperature.[1,3,5,10-15] Additional chemical and physical data for Propylene Carbonate are listed in Table 1.

Propylene Carbonate is manufactured by reacting propylene oxide and carbon dioxide in the presence of a proprietary catalyst. Since the reaction product is at least 99.0% pure, no purification steps are taken. The impurities consist of residual carbon dioxide and possibly some low molecular weight aldehydes and degradation products of Propylene Carbonate.[3]

USE

Noncosmetic Use

Propylene Carbonate is used as an extraction solvent, as a solvent in electrochemistry and electron paramagnetic resonance spectrometry, and as a solvent for various inorganic salts, plasticizers, and synthetic fibers and polymers. Other applications include use as a vehicle in ointments and creams, as a plasticizer, and as a reaction medium. The compound is also used in the organic synthesis of other materials and in gas purification.[10-12,15,19-29]

Federal regulations permit the use of Propylene Carbonate as an adhesive

*An aqueous system that varies much from neutral pH will result in decomposition of Propylene Carbonate. Although there are no specific data on the stability of Propylene Carbonate in saline solution, it is likely that the cosmetic ingredient will decompose in such a solution.[16]

†Upon subcutaneous injection, propylene oxide (1.5 g/kg) induced local sarcomas in rats. Tumors were not seen in organs distant to the injection site.[17]

TABLE 1. Chemical and Physical Data for Propylene Carbonate

Property	*Value*	*Reference*
Molecular formula	$C_4H_6O_3$	1, 4, 5
Molecular weight	102.09	1, 3, 5, 14, 18
Freezing point	−48.8°C −49.2°C (easily super-cooled)	5, 10, 14
Boiling point	241.7°C 242.1°C 243.4°C	5, 10 14 1
Specific gravity	1.203 minimum (20/20°C)	3
Density	1.2069 g/ml (20°/20°C) 1.2057 g/ml (20°/4°C) 1.2049 g/ml (20°/4°C)	5, 14 10 1
Flash point	275°F (135°C) open cup 270°F (132°C) 266°F (130°C) Pensky-Martens	14 5, 10 1
Ignition point	510°C	1
Refractive index	1.4209 (n 20/D) 1.4189	3, 10 5
Vapor pressure	0.03 mm Hg (20°C)	5, 14
Viscosity	2.76 (20°C); 1.62 (50°C) centipoises 1.67 centistokes at 38°C	1 11
Solubility		
In water	8.3%	3
In 2.7 M sodium chloride	0.125 g/ml	15
Dielectric constant	63 69 esu at 23°C	1 11, 12
Weight/gallon	10 lb (20°C)	10
Weight/volume conversion factor	4.17 (mg/m^3 ~ 1 ppm)	5
pH (10% by weight aqueous solution)	6.5–7.5	3
Assay (by gas-liquid chromatography)[a]	98% minimum	18
Assay (by acid titration)	99% by weight minimum	3
Ash content	0.01% maximum	3

[a]Typical assay of one commercially available product.

component in food packaging articles. However, no specific limitations for this indirect food additive use have been established.[30]

Cosmetic Use

Propylene Carbonate is used in cosmetics as a polar additive for montmorillonite or bentonite clay gellants. These gellants are widely used as bases for antiperspirants, lipsticks, skin cleansers, eye shadow, mascara, hair conditioners, and other cosmetic products.[3]

Data submitted to the Food and Drug Administration (FDA) in (or before) 1981 by cosmetic firms participating in the voluntary cosmetic registration program indicated that Propylene Carbonate was used as an ingredient in a total of 295 of the registered cosmetic formulations (Table 2). Product types in which Propylene Carbonate was most frequently used included lipstick (95 products), eye shadow (42 products), and mascara (34 products). Cosmetic formulations contained this ingredient at concentrations of >1–5% (212 products), >0.1–1% (80 products), and ≤0.1% (3 products).[31,32]

Voluntary filing of product formulation data with the FDA by cosmetic man-

TABLE 2. Product Formulation Data for Propylene Carbonate[31,32]

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*		
			>1–5	*>0.1–1*	*≤0.1*
Bath oils, tablets, and salts	237	1	1	–	–
Eyebrow pencil	145	6	6	–	–
Eyeliner	396	17	17	–	–
Eye shadow	2582	42	26	16	–
Eye lotion	13	1	1	–	–
Mascara	397	34	1	33	–
Other eye makeup preparations	230	9	8	1	–
Colognes and toilet waters	1120	5	5	–	–
Perfumes	657	4	4	–	–
Hair conditioners	478	1	1	–	–
Other hair coloring preparations	49	3	3	–	–
Blushers (all types)	819	13	9	3	1
Face powders	555	1	1	–	–
Makeup foundations	740	11	10	1	–
Lipstick	3319	95	85	9	1
Makeup bases	831	13	–	13	–
Makeup fixatives	22	1	1	–	–
Other makeup preparations (not eye)	530	9	8	1	–
Nail creams and lotions	25	1	1	–	–
Other personal cleanliness products	227	4	2	1	1
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	9	9	–	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	1	–	1	–
Moisturizing skin care preparations	747	2	2	–	–
Night skin care preparations	219	4	4	–	–
Skin fresheners	260	1	–	1	–
Suntan gels, creams, and liquids	164	6	6	–	–
Other suntan preparations	28	1	1	–	–
1981 TOTALS		295	212	80	3

ufacturers and formulators conforms to the prescribed format of preset concentration ranges and product catagories as described in Title 21 Part 720.4 of the Code of Federal Regulations.[33] Because data are only submitted within the framework of preset concentration ranges, opportunity exists for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

Cosmetic products containing Propylene Carbonate are applied to or have the potential to come in contact with skin, eyes, hair (scalp), and nails. Small amounts of the ingredient could be ingested from lipstick (Table 2).

Product formulations containing Propylene Carbonate may be used from once a week to several times a day. Many of these products may be expected to remain in contact with body surfaces for as briefly as a few hours to as long as a few days. Each cosmetic product containing Propylene Carbonate has the potential for repeated application over the course of several years (Table 2).

TOXICOLOGY

Acute Oral Toxicity

Five male and female Sprague Dawley rats were administered undiluted Propylene Carbonate at a dose of 5 g/kg by oral gavage. Animals were observed thereafter for 14 days. Salivation was noted immediately after the single dose. None of the rats died, and no lesions were observed at terminal necropsy.[34]

Propylene Carbonate was given by oral intubation in logarithmic doses to groups of five, nonfasted Carworth-Wistar rats. Animals were observed for a period of 14 days following the single oral dose. The methods of Thompson[35] and Weil[36] were used to calculate the LD_{50} and its confidence range. The acute oral LD_{50} was 29.1 g/kg.[37] According to the toxicity classification system of Hodge and Sterner,[38] Propylene Carbonate is "relatively harmless" to rats by oral administration.

The single dose, oral LD_{50} of Propylene Carbonate in male albino mice was 20.7 gm/kg.[39] No other details were reported.

The acute oral toxicity of an experimental underarm stick containing 20% Propylene Carbonate was assessed in 10 Sprague-Dawley rats (5 males, 5 females). The procedures used were those as described in Title 16 Part 1500.3 of the Code of Federal Regulations.[40] The product, as a 25% w/v mixture in corn oil, was given in a single oral dose of 5.0 g/kg. The animals were observed thereafter for 14 days. During the 4 h immediately after administration, males were "sedate" and/or had "dyspnea"; 1 of the 5 males died. The 4 surviving males appeared normal from day 2 to day 14. All females survived and appeared normal throughout the 14-day observation period. Body weight gains were normal for all surviving animals, and no gross lesions were observed in any animal at necropsy.[41]

A cream blush and an antiperspirant each containing 2.0% Propylene Carbonate were evaluated for their acute oral toxicity. Fasted Harlan Wistar rats (five of each sex) were given a single 5 g/kg oral dose of the cream blush as a 25% suspension in corn oil. Poor grooming and soft red stools were observed 3

h after treatment and persisted for 3 days. At the conclusion of the 7-day study, male rats had an average body weight loss of 25 g, whereas the females had gained an average of 37 g.[42] The antiperspirant was administered at a single oral dose of 10 ml/kg by stomach tube to 10 albino rats (5 of each sex). Clinical observations varied among the rats, but none appeared related to Propylene Carbonate. Gaseous distention of the gastrointestinal tract accompanied by darkened mucoid contents was observed in 2 males. A third male had congested kidneys. Females had no lesions at necropsy. All animals survived and had satisfactory body weight gains for the 14-day study. The oral LD_{50} of the antiperspirant was >10 ml/kg.[43]

Three lip products containing Propylene Carbonate were tested for acute oral toxicity in Spraque Dawley rats. The three test materials consisted of two lip slickers (each containing approximately 0.54% Propylene Carbonate) and a lip gloss. The lip gloss was tested at 50% concentration in mineral oil; the lip gloss/mineral oil mixture contained approximately 0.25% Propylene Carbonate. Each test material was given at a single oral dose to a group of 10 adult rat (5 females, 5 males). The two lip slickers were administered by gavage at a dose of 20 ml/kg, whereas the lip gloss/mineral oil mixture was given at a dose of 15 g/kg. The 30 animals were observed for 14 days. No deaths or toxic effects were observed.[44-46]

Eye Irritation

Undiluted Propylene Carbonate (0.1 ml, pH 8.82) was instilled into the right eye of each of three male and three female albino rabbits. Ocular irritation was assessed thereafter according to the method of Draize et al.[47] Average scores at 1 h, 24, 48 h, 72 h, and 7 days were 12.5, 9.8, 5.1, 4.8, and 0.0, respectively, indicating minimal irritation. Of the six rabbits tested, five had irritation of the conjunctivae only, and one had irritation of the cornea, iris, and conjunctiva.[48]

The ocular irritating effects of 10.5, 17.5, and 100% Propylene Carbonate were assessed in three groups of rabbits. A single drop of one of the test materials was placed into the conjunctival sac of one eye of each of three rabbits (three per concentration). The other eye served as an untreated control. Instillations were made daily for 14 consecutive days. Two of three rabbits treated with 100% Propylene Carbonate had a yellow ocular discharge by day 7; no other chemically-induced changes were observed. No ocular irritation was noted in the six rabbits exposed to the two lower concentrations of Propylene Carbonate.[49]

Ocular injury by this cosmetic ingredient was assessed in a second study by the procedures detailed by Carpenter and Smyth.[50] A single instillation of 0.5 ml Propylene Carbonate was moderately irritating to the rabbit eye.[37]

Instillation of 0.5 ml Propylene Carbonate into the conjunctival sac of the eyes of rabbits produced marked erythema of the conjunctivae, vascularization of the sclera, and edema of the lids and nictitating membrane within 24 h. All eyes appeared normal by the seventh day.[39]

Five "organically modified clay mastergels" each containing 3% (w/w) Pro-

pylene Carbonate were evaluated for ocular irritation.* The test procedures used were a modification of those outlined in the *Journal Officiel de la Republique Francaise.*[51,52] A single 0.1 ml dose of the undiluted test material was instilled into the conjunctival sac of the right eye of each of six male, New Zealand rabbits; the left eye of each animal served as an untreated control. Treated eyes received no water rinse. For each of the five test materials, six animals were used per assay (six animals per test material per assay). Eyes were examined for conjunctival, iridial, and corneal lesions 1 h postinstillation, and after 1, 2, 3, 4, and 7 days. Irritation was scored on a scale of 0 (nonirritating) to 110 (extremely irritating) according to the methods described by Kay and Calandra.[53] Scores ranged from 8.5 to 17.17, indicating that the test materials were irritating or "slightly" irritating to the rabbit eye (Table 3).[54,55]

Cosmetic products containing Propylene Carbonate were tested for ocular irritation in eight different studies. In three of the eight tests, groups of six albino rabbits were used to evaluate a blush cream (2% Propylene Carbonate) and two lip slickers (each containing 0.54% Propylene Carbonate). The products were instilled as a single 0.1 ml dose into one eye (six rabbits/product). The exposed eye received no further treatment; the unexposed eye served as untreated control. The rabbits were observed daily for 3–7 days following exposure. Slight conjunctival irritation was noted 1 h after treatment with the blush cream (2% Propylene Carbonate). However, this irritation had dissipated by the 24-h evaluation. The cornea and iris had no signs of irritation.[42] One rabbit also developed conjunc-

*The composition of each "clay mastergel" consisted of 10% w/w clay gellant (either stearalkonium hectorite or quaternium-18 hectorite), 87% w/w solvent (either lanolin oil/isopropyl palmitate, castor oil, isopropyl myristate, mineral spirits, or caprylic/capric triglyceride), and 3% w/w polar additive (Propylene Carbonate).

TABLE 3. Eye Irritation of Clay Mastergels Containing Propylene Carbonate[54,55]

Clay mastergel containing 3% Propylene Carbonate, 10% gellant and 87% (w/w)[a]	*Acute ocular irritation index in albino rabbits (scale: 0–110)*	*Conclusion*
Lanolin oil/isopropyl palmitate	12.67	Slightly irritating
Castor oil	8.5	Slightly irritating
Isopropyl myristate	Assay no. 1: 12.33 (slight corneal opacity in 2/6 rabbits)	Slightly irritating
	Assay no. 2: 14.5 (slight corneal opacity in 1/6 rabbits)	Slightly irritating
Mineral spirits	Assay no. 1: 16.83 (slight corneal opacity in 5/6 rabbits)	Irritating
	Assay no. 2: 17.17 (slight corneal opacity in 3/6 rabbits)	Irritating
Caprylic/capric triglyceride	11.0	Slightly irritating

[a]Single 0.1 ml dose.

tival irritation to one of the two lip slickers (0.54% Propylene Carbonate). This irritation was observed at the 24-h evaluation but had cleared by the 48-h reading.[56] No ocular irritation was observed after exposure to the second lip slicker (0.54% Propylene Carbonate).[57]

In the fourth study, 0.1 g of a lip gloss containing 0.51% Propylene Carbonate was instilled into the conjunctival sac of one eye of each of six female New Zealand rabbits. Three of the exposed eyes received a rinse of aqueous sodium chloride solution 4 seconds after treatment, whereas the other three exposed eyes received no further treatment. Nontreated eyes served as controls. The rabbits were observed 24, 48, and 72 h posttreatment. No eye irritation was noted.[58]

In the fifth of eight studies, 0.1 ml of an eyeliner containing 1.85% Propylene Carbonate was instilled into one eye of each of nine female New Zealand rabbits. The eyes of three of the nine rabbits received no further treatment. The eyes of a second group of three rabbits received a rinse of aqueous sodium chloride solution 2 seconds after instillation of the product, and a third group of three rabbits was given a similar rinse 4 seconds after product exposure. Nonexposed eyes served as untreated controls. Evaluations for irritation were made 24, 48, and 72 h posttreatment. The eyeliner containing 1.85% Propylene Carbonate produced no ocular irritation.[59]

In the sixth study, the procedures described in Title 16 Part 1500.42 of the Code of Federal Regulations[40] were used to evaluate the ocular irritation potential of an experimental underarm stick containing 20% Propylene Carbonate. A single 0.1 g dose of the product was instilled into the conjunctival sac of one eye of each of nine albino rabbits. The untreated eye served as a control. Six of the nine rabbits received no water rinse following instillation; the remaining three rabbits had the treated eye rinsed with water (1000 ml/1 minute) 30 seconds after product exposure. The treated eyes were examined at 1 h, and at 1, 2, 3, and 7 days postinstillation. No lesions of the iris or cornea were observed. Minimal irritation of the conjunctivae was noted in all rabbits. However, this irritation generally decreased in severity over the 7 days and with water rinsing. Average ocular irritation scores for unrinsed eyes were 9.7, 7.7, 4.3, 3.0, and 2.7 at 1 h and at 1, 2, 3, and 7 days, respectively. For rinsed eyes, the average ocular irritation scores over the same time frame were 4.0, 2.0, 2.0, 2.0, and 0.7, respectively. The investigator concluded that the product was "possibly" an ocular irritant.[41]

In the seventh and eighth studies, the Draize[60] procedure was used to assess two antiperspirants, one containing 2.0% Propylene Carbonate and the other 1.67% Propylene Carbonate. For each antiperspirant tested, the product was instilled as a single 0.1 ml dose into one eye of each of 10 New Zealand rabbits. Five of the 10 treated eyes received no water rinse following instillation of the antiperspirant, whereas the other 5 treated eyes were given a water rinse 4 seconds after instillation of the test material. The untreated eyes served as controls. Ocular reactions to each of the two antiperspirants were similar over the 7-day observation period. In those rabbits receiving no water rinse, minimal conjunctival irritation was observed up to 3 and 4 postinstillation. Minimal irritation of the cornea and iris was also evident, but this irritation had dissipated in all instances by the 48-h evaluation. In the rabbits receiving a water rinse, conjunctival and iridial irritation was minimal. Conjunctival irritation persisted no more

than 3 days posttreatment, whereas iridial irritation persisted no more than 1 h posttreatment. No corneal lesions were observed in animals given the water rinse.[61,62]

Inhalation

Smyth et al.[37] determined in a range-finding study that inhalation of the "concentrated vapors" of Propylene Carbonate for 8 h was not lethal to six rats during a 14-day observation period. The vapor concentration of Propylene Carbonate was not reported for this study.

Inhalation tests were conducted with dogs, guinea pigs, and rats by exposing the animals to an aerosol of Propylene Carbonate at a concentration of 2.8 mg/l 6 h/day, 5 days/week for 21 days. The rats developed rhinorrhea and diarrhea. No other toxicological effects were reported.[39]

Muscle Irritation

Propylene Carbonate was evaluated for its ability to produce tissue irritation in chicken pectoral muscle. A volume of 0.5 ml of Propylene Carbonate was injected one-half inch deep into the right and left pectoral muscle of each of six 7–8-week-old male Hubbard Crossbred broilers. A 20-gauge needle was used for the single injection. Two chickens were killed at 1, 3, and 7 days postinjection for necropsy and evaluation of lesions at the injection site. Test sites were evaluated for tissue irritation using a scale ranging from 1 (no visible tissue damage or discoloration) to 5 (necrosis). Scores for the right and left pectoral muscle of each chicken were 5, indicating tissue necrosis. The treated sites had no test material in the tissue.[63]

Subcutaneous Toxicity

Groups of 10 male dd-strain mice were given a single subcutaneous injection of Propylene Carbonate at a dose ranging from 9.6 to 20 ml/kg. Wistar strain male rats were similarly administered a single dose of Propylene Carbonate ranging from 6.7 to 20 ml/kg. Both species were observed for 72 h after treatment, during which time "decreased activities were generally observed." The subcutaneous LD_{50} values were 15.8 and 11.1 ml/kg in mice and rats, respectively.[49]

Skin Irritation

Undiluted Propylene Carbonate (pH 8.8) was applied to the intact and abraded, clipped skin of each of six albino rabbits (three males and three females). Skin responses were assessed at 24 and 72 h after treatment. Very slight to well-defined erythema and very slight edema were noted at the 24-h evaluation. All treated sites were normal at the 72-h evaluation. The Primary Irritation Index was 0.2 (max = 8.0), indicating slight skin irritation.[64]

Propylene Carbonate was evaluated for irritation after topical application to the clipped skin of five albino rabbits. Application of 0.01 ml of the undiluted test material produced slight skin irritation within 24 h.[37]

Five "organically modified clay mastergels" each containing 3% (w/w) Propylene Carbonate were evaluated for skin irritation. The composition of the clay mastergels has been previously described (see Eye Irritation Section). The skin irritation test was conducted by a modification of the procedures described in the *Journal Officiel de le Republique Francaise.*[51,52] Open and/or closed patches containing 0.5 ml of the undiluted test material were applied to abraded and intact clipped skin of male, New Zealand rabbits. For each test material, six animals were used per assay (six animals per test material per assay). After 24 h of contact with the skin, the patches were removed and the test sites were evaluated for erythema and edema. A second evaluation was performed 72 h after application of the test substance. Skin irritation was scored on a scale of 0 (nonirritating) to 8 (severely irritating). The "primary irritation index"* for each of the five test materials ranged from 0 to 3.25, indicating that the five materials were either nonirritating, "slightly" irritating, or "moderately" irritating to the skin of albino rabbits (Table 4).[54,55]

In seven separate experiments, cosmetic products formulated with 0.51–20% Propylene Carbonate caused slight to moderate skin irritation in rabbits. These studies are described below.

The methods described in Title 16 Part 1500.41 of the Code of Federal Regulations[40] were used to assess the skin irritation potential of an experimental underarm stick containing 20% Propylene Carbonate. The product was applied to the abraded and intact skin of each of six albino rabbits. The treated sites were covered with gauze patches, which were secured to the rabbit by an impervious plastic sleeve wrapped around the animal's trunk. The gauze dressings were removed after 24 h, and the treated sites were evaluated for erythema and edema at 24 and 72 h postapplication. Four of six rabbits had slight erythema; one of six rabbits had slight edema. The Primary Irritation Index for the underarm stick was 0.46, indicating potential for slight irritation.[41]

*The primary irritation index is a value depicting the average score for intact and abraded skin at both 24 and 72 h for the test group as a whole.

TABLE 4. Primary Skin Irritation of Clay Mastergels Containing Propylene Carbonate[54,55]

Clay mastergel containing 3% Propylene Carbonate, 10% gellant and 87% (w/w)	*Primary irritation index in albino rabbits (scale: 0–8)*	*Conclusion*
Lanolin oil/isopropyl palmitate	1.25 (closed 24-h patch)	Slightly irritating
Castor oil	1.83 (closed 24-h patch)	Slightly irritating
Isopropyl myristate	Assay no. 1: 0.92 (closed 24-h patch)	Slightly irritating
	Assay no. 2: 1.08 (closed 24-h patch)	Slightly irritating
	Assay no. 3: 0.00 (open 24-h patch)	Nonirritating
Mineral spirits	Assay no. 1: 2.83 (closed 24-h patch)	Moderately irritating
	Assay no. 2: 3.25 (closed 24-h patch)	Moderately irritating
	Assay no. 3: 2.17 (open 24-h patch)	Moderately irritating
Caprylic/capric triglyceride	0.83 (closed 24-h patch)	Slightly irritating

In a second study, a blush cream (0.5 ml) containing 2.0% Propylene Carbonate was applied daily for 4 days to the shaved back of three albino rabbits. Slight edema and dehydration were observed on day 6 and 7 of a 7-day observation period. The "irritation index" was 0.3 on a scale of 0 (no irritation) to 8.0 (corrosive), indicating slight skin irritation.[42]

In a third study, an antiperspirant with 2.0% Propylene Carbonate was applied for 24 h under a "plastic binder" to the clipped, intact skin of four New Zealand rabbits. The initial skin reaction consisted of slight to moderate erythema accompanied by slight edema. The edema completely subsided by day 5 posttreatment and the erythema by day 6. Slight to moderate desquamation developed in all animals on day 5 and persisted until day 12 posttreatment.[65]

An antiperspirant containing 2.0% Propylene Carbonate and an antiperspirant containing 1.67% Propylene Carbonate were evaluated in a fourth and fifth study, respectively. In each study, the formulation was applied for 24 h under an occlusive dressing to the clipped skin of four New Zealand rabbits. The 0.5 ml applications were made to both abraded and intact sites. Irritation was scored on a scale of 0 (no irritation) to 8.0 (corrosive), according to the method of Draize.[60] The primary irritation index was 0.94 for one antiperspirant (2.0% Propylene Carbonate) and 0.88 for the other (1.67% Propylene Carbonate), indicating in both instances slight skin irritation.[66,67]

A lip slicker containing 0.54% Propylene Carbonate and a lip gloss containing 0.51% Propylene Carbonate were evaluated for skin irritation in a sixth and seventh study, respectively. Each lip product was applied in daily doses of 0.5 ml or 0.5 g for 3 days to the clipped skin of six female New Zealand rabbits. Open patches were used for each of the applications. Two rabbits developed slight skin erythema to the lip gloss by the 24-h evaluation; no irritation was noted in these animals at the 48-h evaluation. Similarly, two rabbits had slight erythema to the lip slicker at the 24- and 48-h evaluations; this irritation had cleared by the 72-h evaluation.[68,69]

Acute Dermal Toxicity

Undiluted Propylene Carbonate was applied in a single 2 mg/kg dose to the abraded skin of five male and five female albino rabbits. The treated sites were covered with gauze and a rubber dam to retard evaporation of the test material. After 24 h, the dressings were removed, and the rabbits were observed thereafter for 14 days. Slight skin erythema was noted in every animal on day 2; however, on day 3, all treated sites appeared normal. None of the rabbits died, and all had normal weight gain. No lesions were observed at necropsy.[70]

The acute dermal LD_{50} of Propylene Carbonate in rabbits was >5 gm/kg. Details of the test procedure were not available.[39]

The acute dermal toxicity and skin penetration of Propylene Carbonate were evaluated by the 24-h plastic sleeve method described by Draize et al.[47] The undiluted material was applied under an impervious plastic sleeve to the clipped skin of each of four male New Zealand albino rabbits weighing 2.5–3.5 kg. Approximately one tenth of the body surface was in contact with the test agent. However, doses of >20 ml/kg could not be retained in contact with the skin. After 24 h, the plastic sleeve was removed from the test site. The animals were

then observed for 14 days to assess mortality. The acute dermal LD_{50} was >20 ml/kg.[37]

A similar procedure involving application of the test material beneath a plastic binder was employed in a second study to assess the dermal toxicity of an antiperspirant containing 2.0% Propylene Carbonate. A single 24-h exposure of the clipped, intact skin of two male and two female albino rabbits to 10 ml/kg of the undiluted product caused "slight depression" but no deaths. After an "initial weight loss during the exposure period," all animals gained weight "satisfactorily." One rabbit developed "slightly labored respiration," which persisted until day 3 posttreatment. Ataxia was observed in two rabbits on days 5 and 6 posttreatment. The acute dermal LD_{50} of the antiperspirant was >10 ml/kg.[65]

An experimental underarm stick containing 20% Propylene Carbonate was evaluated for acute dermal toxicity. The method used was that as described in Title 16 Part 1500.40 of the Code of Federal Regulations.[40] The product was applied as a single 2.0 g/kg dose to the clipped skin of the back of 10 albino rabbits. The skin of five animals was abraded (two males and three females), whereas the skin of the remaining animals was intact (three males and two females). Treated sites were covered with gauze patches, which were secured to the body by means of an impervious plastic sleeve. The gauze dressings were removed after 24 h. All animals survived and "appeared normal" throughout the 14-day observation period. Slight to mild skin erythema was observed upon patch removal, and small body weight loss was noted in one male and one female during the last 7 days of the study. Gross examination of organs revealed "pitted kidneys" in one male and one female, and "hemorrhagic focal areas" in the kidneys of another male. No gross lesions were reported in the remaining seven animals.[41]

Subchronic Dermal Toxicity

The subchronic dermal toxicity of 3.5, 10.5, and 17.5% Propylene Carbonate in physiological saline was evaluated by Kuramoto et al.[49] Each test material was applied to the clipped backs of male Wistar rats daily, 6 days a week for 1 month. A control group was similarly treated with 10% physiological saline. Microscopic changes in skin samples included hyperkeratosis and an increase in number of basal cells at the treated sites in the rats of the two high concentration groups. Gross examination of the salivary glands, stomach, and intestine and microscopic examination of the brain, lung, heart, kidneys, spleen, adrenals, stomach, epidermis, intestine, testicles, thyroid, and sperm duct were negative for exposure-related effects in treated rats. No differences were noted between treated animals and controls with respect to behavior, feed and water intake, body weight gain. organ weights, hematological values (hematoglobin, hemocrit, red and white blood cell count), blood chemistry parameters (alkaline phosphate, sugar, serum, protein, serum transaminase), and urinalysis (volume, pH, sugar).

Subchronic dermal applications of Propylene Carbonate at a dose of 1000 mg/kg daily to rabbits for a 2-week period "failed to produce pharmacotoxic effects or pathological changes." No other details of this study were available.[39]

Cumulative Skin Irritation

The cumulative skin irritating ability of each of five "organically modified clay mastergels" was determined by a modification of the procedures outlined in the *Journal Officiel de la Republique Francaise.*[51,52] The composition of the clay mastergels, each containing 3% (w/w) Propylene Carbonate, has been previously noted (see Eye Irritation Section). The undiluted test material was applied in a 2 ml daily dose, 5 days a week, for 6 weeks to the clipped flanks of three male New Zealand rabbits. The test substance was spread uniformly over the skin by hand, and the skin then was given a light massage for 30 seconds "to ensure maximal penetration" of the material. Excess material was removed by gauze. The treated skin was examined daily for erythema, edema, thickening, dryness, and hair growth. Body weight was recorded each week. After 6 weeks, two biopsies were taken from the treated skin of each animal. A scale of 0 (no skin irritation) to 8 (severe skin irritation) was used for calculation of the "mean maximum irritation index." Scores ranged from 1.67 to 2.67, indicating that the test materials were "slightly" irritating to "moderately" irritating to albino rabbit skin (Table 5). On the basis of macroscopic and microscopic examinations of the treated skin, the investigators concluded that the test materials were "relatively well tolerated" or caused "slight intolerance."[54,55]

MUTAGENICITY AND GENOTOXICITY

Propylene Carbonate was evaluated at physiological pH 7.4 for mutagenicity in *Salmonella typhimurium*. Strains TA1535, TA1537, TA1538, TA98, and TA100 were tested with and without metabolic activation by liver hemogenate from

TABLE 5. Cumulative Skin Irritation of Clay Mastergels Containing Propylene Carbonate[54,55]

Clay mastergel containing 3% Propylene Carbonate, 10% gellant and 87% (w/w)[a]	*Mean Maximum Irritation Index in albino rabbits (scale: 0–8)*	*Conclusion*
Lanolin oil/isopropyl palmitate	1.67	Slightly irritating; test material was "relatively well tolerated"
Castor oil	2.00	Slightly to moderately irritating; test material was "relatively well tolerated"
Isopropyl myristate	2.67	Moderately irritating; test material elicited an orthoergic reaction and caused "slight intolerance"
Mineral spirits	2.00	Slightly to moderately irritating; test material caused "slight intolerance"
Caprylic/capric triglyceride	2.00	Slightly to moderately irritating; test material was "relatively well tolerated"

[a]Applied in a 2 ml daily dose 5 days a week for 6 weeks.

Aroclor 1254-treated rats. For the liquid preincubation modification of the Ames assay, doses of 50–5000 μg/plate were used. At these doses, Propylene Carbonate was inactive as a mutagen in four tester strains. In the case of TA100, Propylene Carbonate showed some minor activity with and without metabolic activation at all five doses; however, a dose-response relationship was not observed.[71]

Propylene Carbonate at five doses up to 4000 μg/plate was negative for genotoxicity in rat hepatocyte primary culture.[72]

CLINICAL ASSESSMENT OF SAFETY

In clinical studies, undiluted Propylene Carbonate caused moderate skin irritation, whereas 5 and 10% Propylene Carbonate in aqueous solution produced no skin irritation or sensitization. An ethanol solution containing 20% Propylene Carbonate produced minimal to moderate skin irritation in human subjects. Cosmetic products or gels containing 0.54–20% Propylene Carbonate were essentially nonsensitizing and, at most, moderately irritating to human skin. Products formulated with 1.51–20% Propylene Carbonate were generally nonphototoxic and nonphotosensitizing. However, one product containing 20% Propylene Carbonate may have produced a low level photoallergic reaction in 1 of 25 subjects tested. These clinical studies are discussed below, and results are summarized in Table 6.

Undiluted Propylene Carbonate was evaluated for skin irritation on a panel of five white, male and female college students. The test material (100 μl) was pipetted onto a cloth disc, which was then sealed to scarified skin by a water-permeable, nonocclusive tape. Applications of Propylene Carbonate were made once daily for 3 days. Readings were made every 24 h, however, the 72-h reading (made 30 minutes after disc removal) was the one used for calculation of scores. Skin reactions were graded on a 5 point scale from 0 (no irritation) to 4 (confluent, severe erythema sometimes associated with edema, necrosis, or bulla formation). Mean scores at the 72-h reading for each subject were in the range of 1.5–2.4, indicating moderate skin irritation.[73]

No skin irritation, fatiguing, or sensitization was observed when two groups of panelists were exposed in a repeated insult patch test to an aqueous solution containing either 5 or 10% by weight Propylene Carbonate. The test procedure required 15 occlusive patches per subject. Fifty subjects were tested at each concentration. No other details of the procedure were available.[74,75]

Twenty-six panelists were used to evaluate the cumulative irritation potentials of an experimental underarm stick and an ethanol solution each containing 20% Propylene Carbonate. Prior to application, the test materials (0.2 g or 0.2 ml) were placed onto patches for 30 minutes to allow evaporation of volatile materials. Patches were applied daily (Monday–Friday) to the skin of the back for a total of 21 applications. Skin reactions of the subjects treated with the underarm stick ranged from "minimal" or "uniform" erythema (the majority of panelists) to "bright red" erythema (3 subjects). Dryness, hyperpigmentation, mild edema, and vesicles of the skin were also observed in a few subjects. Twelve panelists had skin reactions to the ethanol–Propylene Carbonate solution. Of these 12 re-

TABLE 6. Clinical Studies

Type of test	*Test material*	*Propylene Carbonate concentration (%)*	*No. of subjects*	*Method*	*Results*	*Reference*
Skin irritation	Propylene Carbonate	100	5	Test material applied to scarified skin once daily for 3 days	Moderate skin irritation	73
Skin irritation/ sensitization	Aqueous solution containing Propylene Carbonate	10	50	Repeat insult patch procedure (15 occluded patches per subject)	No skin irritation, fatiguing, or sensitization	75
Skin irritation/ sensitization	Aqueous solution containing Propylene Carbonate	5	50	Repeat insult patch procedure (15 occluded patches per subject)	No skin irritation, fatiguing, or sensitization	74
Cumulative skin irritation	Ethanol solution	20	26	Patches containing test material applied to skin daily for total of 21 applications	Twelve subjects developed "minimal" to "bright red" erythema. Occasional hyperpigmentation and dryness also noted	76
Cumulative skin irritation	Underarm stick	20	26	Patches containing product applied to skin daily for total of 21 applications	"Minimal" to "bright red" erythema observed. Occasional hyperpigmentation, dryness, edema, and vesicles of the skin also reported	76

TABLE 6. (Continued)

Type of test	*Test material*	*Propylene Carbonate concentration (%)*	*No. of subjects*	*Method*	*Results*	*Reference*
Skin irritation/ sensitization	Underarm stick	20	91	Repeat Insult Patch Procedure: Product applied to skin under 10 consecutive 48-h patches. After 14 days, a 48-h challenge patch applied	Reactions during induction phase ranged from "barely perceptible" erythema to "definite" erythema. Ten subjects developed reactions to challenge patch; however, most of these reactions were "barely perceptible" or "doubtful." Results of rechallenge testing were negative for sensitization in 2 of 3 subjects; the third subject had a "doubtful" reaction to the rechallenge patch	77
Skin irritation/ sensitization	Gel (A)	3.5	54	Gel applied under 24-h patch to skin every other day for total of 10 induction applications. After 14 days, 24-h challenge patch applied	No skin irritation or sensitization	79
Skin irritation/ sensitization	Gel (B)	3.5	49	Gel applied under 24-h patch to skin on Mon., Wed., and Thurs. for total of 15 induction applications. After 17 days, 24-h challenge patch applied	No skin irritation or sensitization	78

Skin irritation/ sensitization	Two gels (C and D)	3.5	51	Gel applied under 24-h patch to skin on Mon., Wed., and Thurs. for total of 15 induction applications. After 17 days, 24-h challenge patch applied	No skin irritation or sensitization to gel C. Gel D caused skin erythema and/or edema in 2 subjects during induction phase. Investigator suggested these reactions were indicative of "fatiguing," and concluded that gel D was a cumulative irritant or fatiguing agent	80
Skin irritation/ sensitization	Cream blush	2.0	210	Shelanski/Jordan Repeat Insult Patch Test: Product applied under 24-h patch to skin every other day for total of 10 induction applications. After 10–14 days, 48-h challenge patch applied. A second 48-h challenge patch applied 7–10 days after initial challenge	Two subjects developed single, 2+ skin reactions (erythema and papules) during induction phase. Investigator suggested these reactions were "nonspecific irritation" and concluded that the cream blush was neither a strong irritant nor a contact sensitizer	81
Skin irritation/ sensitization	Antiperspirant	2.0	51	Modification of Draize[60] procedure: 24-h patches containing product applied to abraded and intact skin every other day for 3 weeks for total of 9 induction applications. A 24-h challenge patch applied in the sixth week of study	Four subjects developed skin erythema on intact sites and four other subjects developed erythema on abraded sites during induction phase. No skin reactions to challenge patch were observed	82

TABLE 6. (Continued)

Type of test	*Test material*	*Propylene Carbonate concentration (%)*	*No. of subjects*	*Method*	*Results*	*Reference*
Skin sensitization	Eyeliner	1.85	210	Occlusive patch containing product applied every other weekday for 3 weeks. After 2 weeks, 2 consecutive 48-h challenge patches applied	No skin sensitization	84
Skin sensitization	Lip slicker	0.54	206	Occlusive patch containing product applied every other weekday for 3 weeks. After 2 weeks, 2 consecutive 48-h challenge patches applied	No skin sensitization	83
Skin irritation/ sensitization/ photosensitization	3 eye area products	1.51–1.98	304	Schwartz and Peck[85] with UV exposure: induction phase consisted of a single 48-h closed patch and a single 48-h open patch. The challenge exposure consisted of a second set of 48-h open and closed patches 10–14 days after the induc- phase. Closed patch sites were irradiated with UV light following both induction and challenge evaluations	During induction phase, weak nonvesicular reactions (9 subjects) and a bullous/ulcerative reaction (1 subject) observed following application of closed patch; no reactions observed as a result of open patch or UV exposure. During challenge phase, 2 subjects had weak nonvesicular reactions to closed patch and 4 subjects had reactions to UV light; no reactions to open patch observed. Investigator concluded products were nonirritating, nonsensitizing, and nonphotosensitizing	87

Skin irritation/ sensitization/ photosensitization	3 eye area products	1.51–1.98	149	Shelanski and Shelanski[88] with UV exposure: both a 24-h open and closed patch containing product applied to skin every other day for total of 10 open induction applications and 10 closed induction applications. After each induction patch, skin remained untreated for 24 h. Two to 3 weeks after induction phase, open and closed challenge patches were applied for 48 h. Closed patch sites exposed to UV light after 1st, 4th, 7th, and 10th induction patches and after challenge patch	Weak, nonvesicular reactions observed in some subjects (2 to 6 reactors per evaluation) during both induction and challenge phases at closed patch sites. A single edematous/vesicular reaction was also noted during induction phase on closed patch site. No observed skin reactions to open patches or to UV light. Investigator concluded products were nonirritating, nonsensitizing, and nonphotosensitizing	87
Phototoxicity	Underarm stick	20	10	Product applied to skin for 24 h under semi-occlusive patch. Following removal, treated sites irradiated with UV light (320–400 nm)	No evidence of phototoxicity	89

TABLE 6. (Continued)

Type of test	*Test material*	*Propylene Carbonate concentration (%)*	*No. of subjects*	*Method*	*Results*	*Reference*
Photoallergenicity	Underarm stick	20	25	During induction phase, product applied to skin twice a week under semioccclusive patches for total of 6 induction applications. Twenty-four h after each induction patch, induction sites exposed to UVA and UVB irradiation (290–400 nm). Following 7 day nontreatment period, challenge patch applied to previously unexposed site. Twenty-four h after challenge patch, challenge site exposed to UVA irradiation (320–400 nm)	No evidence of phototoxicity in 24 of 25 subjects; however, one subject had a "possible low level" photoallergic reaction	90

actors, 11 had "minimal" skin erythema and one had "bright red" erythema. Also noted among the 12 panelists were occasional hyperpigmentation and dryness. One subject was noted as having "a rather explosive reactivity pattern" to both test materials, which suggested the possibility of an "angry-back syndrome" (or "presensitization" reaction). The experimental underarm stick and the ethanol–Propylene Carbonate solution were given "cumulative irritation" ratings of 276.5 and 66.0, respectively, out of a maximum possible score of 2184 (26 subjects × 21 days × max irritation score of 4). The negative control (baby oil) had a cumulative irritation index of 4.5.[76]

An experimental underarm stick containing 20% Propylene Carbonate was evaluated in a repeated insult patch test for skin irritation and sensitization. The test group consisted of 91 men and women between the ages of 18 and 78. This group was predominantly white but also included hispanics, blacks, and Asians. The induction phase was initiated by applying occlusive patches containing the test material (200 mg). However, after three applications, "it became apparent" that the product was too irritating to be tested under occlusive (closed) conditions. Testing was resumed on a new site using 50 mg of product and semi-occlusive (open) patches. Induction applications consisted of 10 consecutive, 48-h patches; patches applied on Friday remained in place for 72 h. A 14-day nontreatment period followed the tenth induction application. The challenge application consisted of a single patch applied for 48 h to a previously unexposed site. Skin responses to the challenge patch were assessed 48 and 72 h after product application. Reactions during the induction phase generally ranged from "barely perceptible" ("doubtful") to "definite" erythema. Occasional edema also was noted in some individuals. Ten subjects developed skin reactions to the challenge patch. Of these 10 reactors, 6 had barely perceptible (doubtful) erythema and 4 had definite erythema or minimal edema. Of these latter 4 reactors (subjects A, B, C, and D), 3 (A, B, C) agreed to a rechallenge test. The results of the rechallenge test were negative in subjects B and C for sensitization; subject A developed barely perceptible (doubtful) erythema to the rechallenge patch. The investigator concluded that the experimental underarm stick containing 20% Propylene Carbonate produced no sensitization under conditions of this test.[77]

Four different gels (A, B, C, and D) each containing approximately 3.5% Propylene Carbonate were tested for skin irritation and sensitization. Gel A was applied under an occlusive 24-h patch to the upper arm or back of 54 subjects (3 males, 51 females). Patches were applied every Monday, Wednesday, and Friday for a total of 10 applications. After a 14-day nontreatment period, a 24-h challenge patch was applied to the original contact site. Skin sites were examined 48 h after the challenge application. A different test procedure was used for gels B, C, and D. For each of these three materials, 24-h occlusive patches were applied on Mondays, Wednesdays, and Thursdays for a total of 15 induction applications. Following a 17-day nontreatment period, a 24-h challenge patch was applied to the original contact site. Exposed sites were examined 48 h after the challenge application. Gel B was applied to a panel of 49 subjects (9 males, 40 females), whereas gels C and D were applied to a group of 51 panelists (5 males, 46 females). Of the 154 subjects exposed to the four gels, 2 developed skin reactions to gel D. Skin responses of these 2 reactors consisted of slight to well-defined skin erythema at the fourth and fifth induction evaluation in one

person and erythema and edema at the tenth induction evaluation in the second person. The investigator suggested that these skin reactions were indicative of "fatiguing," since they occurred later than the first induction application and did not recur when the contact site was changed. It was concluded that gel D containing 3.5% Propylene Carbonate was a cumulative irritant or a fatiguing agent.[78-80]

A Shelanski/Jordan Repeat Insult Patch Test was conducted to determine the skin irritation and sensitization potential of a cream blush formulated with 2.0% Propylene Carbonate. An occlusive gauze dressing containing the product was applied for 24 h to the upper back of each of 210 subjects. Applications were made every Monday, Wednesday, and Friday for 3½ weeks for a total of 10 induction patches. Ten to 14 days after the last induction application, a 48-h challenge patch was applied. A second 48-h challenge patch was applied 7–10 days after the initial challenge patch. Skin responses were graded on a scale of 0 (no reaction) to 4+ (marked edema and vesicles). Two individuals developed single, 2+ reactions (erythema and papules). One of these reactions was observed at the sixth induction evaluation, whereas the second reaction was observed at the ninth induction evaluation. These two reactions were reported as "nonspecific irritation." No other skin reactions were noted during the induction or challenge phases. It was concluded that the cream blush was "neither a strong irritant nor a contact sensitizer."[81]

An antiperspirant containing 2.0% Propylene Carbonate caused "essentially no irritation" and no sensitization in a repeat insult patch test involving 51 adult Caucasion panelists (19 males and 32 females). A modification of the procedure described by Draize[60] was used. Occlusive patches containing 0.5 ml of the product were applied for 24 h to abraded and intact sites of the upper arm every Monday, Wednesday, and Friday for 3 consecutive weeks (nine induction applications). In the sixth week, a challenge patch was applied for 24 h to the original intact site, as well as to a previously untreated site. Four people had skin erythema on intact sites, and four other subjects had erythema on abraded sites at various grading sessions throughout the induction period. These reactions persisted for no more than one or two evaluations. No reactions to the challenge patches were observed.[82]

An eyeliner and lip slicker containing approximately 1.85% and 0.54% Propylene Carbonate, respectively, were evaluated for their ability to produce skin sensitization. Two hundred six subjects were tested with the lip slicker, whereas 210 subjects were tested with the eyeliner. Occlusive patches containing the products were applied to the upper back on Monday, Wednesday, and Friday for 3 consecutive weeks. At the conclusion of this induction phase, a 2-week nontreatment period ensued, followed by two consecutive 48-h challenge patches. Challenge patches were applied to the original induction site and to an adjacent site. Skin responses were graded 48 and 96 h after challenge. No sensitization was observed to either product.[83,84]

Three hundred four panelists were used to assess the skin irritating, sensitizing, and photosensitizing effects of three "eye area products" each containing between 1.51 and 1.98% Propylene Carbonate. The test procedures employed were those as described by Schwartz and Peck,[85] whereas skin reactions were graded according to the scoring system outlined by Wilkinson et al.[86] For the induction phase, a single closed patch and a single open patch were applied for

48 h to the skin of each subject. The challenge exposure consisted of a second set of 48-h open and closed patches 10–14 days after the induction phase. Closed patch sites were irradiated with ultraviolet (UV) light following both induction and challenge gradings. The light source consisted of a Spectronics B-100 broad-spectrum lamp, which included in its spectrum a wavelength of 365 nm. The lamp was held 12 inches from the skin for 1 minute. Of the 304 panelists evaluated during the induction phase, 9 had "weak" (nonvesicular) reactions and 1 had an "extreme" (bullous or ulcerative) reaction to the closed patch. No reactions were observed as a result of the open induction patch or as a result of UV exposure. Of the 304 subjects assessed during the challenge phase, 2 had weak, nonvesicular reactions to the closed patch, whereas 4 developed skin reactions to the UV light; no reactions to the open challenge patches were observed. It was not ascertained whether the few positive reactions to the exaggerated closed patch conditions and to the UV light were due to Propylene Carbonate or other ingredients in the product. The three eye area products were considered by the investigator to be nonirritating, nonsensitizing, and nonphotosensitizing under conditions of the test.[87]

The same three eye area products were tested in a second study on 149 subjects by means of a repeat insult patch procedure involving UV exposure. The test methods and grading of skin reactions were as described by Shelanski and Shelanski[88] and Wilkinson et al.,[86] respectively. Both open and closed patches containing the product (1.51–1.98% Propylene Carbonate) were applied for 24 h to the skin every other day for a total of 10 open induction applications and 10 closed induction applications. Between application of each induction patch, the skin remained untreated for 24 h. Two to three weeks after the tenth induction patch, open and closed challenge patches were applied to the skin for 48 h. Closed patch sites were exposed to UV light following grading of the first, fourth, seventh, and tenth induction patches, as well as following the challenge patch. The light source consisted of a Spectronics B-100 broad-spectrum lamp, which included in its spectrum a wavelength of 365 nm. The light was held 12 inches from the skin for 1 minute. Weak, nonvesicular reactions were observed in a few subjects (2–6 reactors/evaluation) during both induction and challenge phases, but those reactions were limited to the closed patch sites. A single, "strong" reaction (edematous or vesicular) was also noted during the sixth and seventh induction grading on the closed patch site. No skin reactions were observed to either the open patches or to the UV light. In the opinion of the investigators, the three eye area products containing 1.51–1.98% Propylene Carbonate were nonirritating, nonsensitizing, and nonphotosensitizing to the skin.[87]

No phototoxicity was observed when subjects were exposed to both UV irradiation and an experimental underarm stick product formulated with 20% Propylene Carbonate. The product (50 mg) was applied under semiocclusive (open) patches to the skin of the back of 10 subjects (male and female Caucasions aged 23–71). Twenty-four hours later, the patches were removed. Sites treated with the product were then irradiated for 12 minutes with a filtered light source (Xenon Arc Solar Simulator (150 W) with a continuous emission spectrum in the UVA and UVA range, 290–400 nm and a Schott WG 345 filter, which screens erythemogenic wavelengths, UVB: 290–320 nm) having an emission spectrum of 320–400 nm. Skin responses were evaluated 24 and 48 h after UV exposure. At the 48-h evaluation, hyperpigmentation was observed in 8 of 10 panelists at sites

treated with both UV light and product, as well as on sites treated with irradiation alone; 2 panelists had no skin reactions. Reactions were similar at the 24-h evaluation. No skin reactions were noted at 24 or 48 h on sites treated with the underarm stick alone. The investigator concluded that there was no evidence of phototoxicity to the underarm stick.[89]

The same experimental underarm stick (20% Propylene Carbonate) was evaluated on 25 subjects for photoallergenicity. The panelists consisted of male and female Caucasions between the ages of 18 and 75. For the induction phase, the product (50 mg) was applied twice weekly (Monday and Thursday) under a semiocclusive patch to the skin of the back of each panelist. A total of six induction applications were made. Twenty-four hours after each induction application, the treated sites were exposed to a dose of three times the individual's MED (minimal erythema dose). The light source consisted of a Xenon Arc Solar Simulator (150 W), which had an emission spectrum in the UVA and UVB range (290–400 nm). Following a 7-day nontreatment period, challenge patches containing the product were applied to previously unexposed sites. Twenty-four hours later, the challenge patches were removed and the treated sites were exposed for 3 minutes to UVA irradiation (320–400 nm). Skin responses for the challenge phase were evaluated 24 h after product application, and 24, 48, and 72 h after irradiation. Of the 25 panelists, 14 developed skin reactions during the challenge phase. Of the 14 reactors, 9 had "minimal" (or "doubtful") erythema, 2 had "hyperpigmentation", and 3 had "mild" to "moderate" erythema. These latter 3 reactors (individual's A, B, and C) also had hyperpigmentation or varying degrees of edema. Of these 3 reactors, 2 (B, C) had reactions on nonirradiated control sites as well (product exposure only). No reactions were noted in any of the 25 subjects on irradiated control sites (UVA exposure only). One reactor (A) completed a rechallenge test. This person developed reactions that "probably" represented photoirritation, but a "low level" photoallergy "could not be excluded." The investigator concluded that there was no evidence of photoallergy in 24 of 25 subjects. Results of the induction phase were not reported.[90]

SUMMARY

Propylene Carbonate is a nonviscous, clear liquid that is partially soluble in water. It is manufactured by reacting propylene oxide and carbon dioxide in the presence of a catalyst. The reaction product has a purity of 99% or greater. Impurities consist of carbon dioxide and possibly some low molecular weight aldehydes. If an acid, base, or salt is present in the aqueous solution of Propylene Carbonate, decomposition will occur.

Noncosmetic applications of Propylene Carbonate include use as a solvent and as an indirect food additive (adhesive component) in food packaging articles. In cosmetics, Propylene Carbonate is used as a polar additive for montmorillonite or bentonite clay gellants. These gellants are used as bases for antiperspirants, lipsticks, skin cleansers, eye shadow, mascara, hair conditioners, and other cosmetic products.

In 1981, Propylene Carbonate was reported under the FDA voluntary cosmetic registration program to be used as a cosmetic ingredient in a total of 295

cosmetic products at concentrations ranging from ≤0.1% to 5% Cosmetic products containing this compound are applied to or have the potential to come in contact with skin, eyes, hair (scalp), and nails. Small amounts of Propylene Carbonate could be ingested from lipstick.

Undiluted Propylene Carbonate produced minimal to moderate ocular irritation and slight skin irritation in studies with rabbits. In an acute dermal toxicity study, slight erythema was noted on the abraded skin of rabbits treated with 2 mg/kg of undiluted Propylene Carbonate; however, no lesions were observed at necropsy. In a second acute dermal toxicity study, the dermal LD_{50} in rabbits of undiluted Propylene Carbonate was >20 ml/kg. Salivation was noted in rats given undiluted Propylene Carbonate in a single 5 g/kg oral dose. The single-dose, oral LD_{50} in rats and mice was 29.1 and 20.7 g/kg, respectively, whereas, the subcutaneous LD_{50} in rats and mice was 11.1 and 15.8 ml/kg, respectively. Undiluted Propylene Carbonate was nontoxic by inhalation to dogs and guinea pigs in a 21-day study but caused rhinorrhea and diarrhea in rats. Daily application of 10.5 or 17.5% Propylene Carbonate in physiological saline to the skin of rats for 1 month produced hyperkeratosis and an increase in the number of basal epithelial cells at the treatment site. Propylene Carbonate was negative for mutagenicity in the Ames *Salmonella*/Microsome Liquid Pre-incubation Assay, and negative for genotoxicity in the Rat Hepatocyte Primary Culture/DNA Repair Test.

In clinical studies, undiluted Propylene Carbonate caused moderate skin irritation, whereas 5 and 10% Propylene Carbonate in aqueous solution produced no skin irritation or sensitization. Cosmetic products or gels containing 0.54–20% Propylene Carbonate were essentially nonsensitizing and, at most, moderately irritating to human skin. Products formulated with 1.51–20% Propylene Carbonate were generally nonphototoxic and nonphotosensitizing. However, one product containing 20% Propylene Carbonate may have produced a low level photoallergic reaction in 1 of 25 subjects tested.

DISCUSSION

Propylene Carbonate is generally used in cosmetics at concentrations ranging from ≤0.1% to 5.0%. Clinical studies indicated that Propylene Carbonate concentrations of 5 and 10% in aqueous solution were nonirritating and nonsensitizing. Undiluted Propylene Carbonate was moderately irritating. In several instances throughout this safety review, reference was made to an experimental underarm stick containing 20% Propylene Carbonate. This product is not marketed for consumer use and contains a concentration of Propylene Carbonate that may be irritating to human skin.

CONCLUSION

On the basis of the available data, the CIR Panel concludes that Propylene Carbonate is safe as a cosmetic ingredient in the present practices of use and concentration.

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REFERENCES

1. GEIGER, F. (1972). New raw materials and adjuvants. Drugs Made in Germany **15**(1), 34.
2. ESTRIN, N.F., CROSLEY, P.A., and HAYNES, C.R. (eds.). (1982). *CTFA Cosmetic Ingredient Dictionary*, 3rd ed. Washington, D.C.: Cosmetic Toiletry and Fragrance Assoc., p. 260.
3. COSMETIC, TOILETRY and FRAGRANCE ASSOCIATION. (November 3, 1982). Submission of unpublished data by CTFA. Cosmetic Ingredient Chemical Description. Propylene Carbonate. Code No. 2-24-1.*
4. FAIRCHILD, E.J. (ed.). (1977). *Registry of Toxic Effects of Chemical Substances.* U.S. Department of Health, Education and Welfare. National Institute for Occupational Safety and Health, Vol. II., p. 283, No. FF96500.
5. SANDMEYER, E.E., and KIRWIN, C.J. (1981). Cyclic Carbonates. In: *Patty's Industrial Hygiene and Toxicology*, 3rd rev. ed. G.D. Clayton and F.E. Clayton (eds). New York: John Wiley and Sons, Vol. 2A:2354,58.
6. SCHULTE, E., SCHULTE, G., and MRONGOVIUS, R.I. (1980). Precutaneous absorption of 3H-pethidine in the rat. Arzneim-Forsch. **30**(2), 267–70.
7. NATIONAL LIBRARY OF MEDICINE. (1983). MEDLARS On-Line Computer System: Chemline and RTECS. Bethesda, MD.: U.S. Department of Health and Human Services, National Institutes of Health.
8. GRANT, J. (ed.). (1969). *Hackh's Chemical Dictionary*, 4th ed. New York: McGraw-Hill Book Co., pp. 624–5.
9. LAPEDES, D.N. (ed.). (1978). *Dictionary of Scientific and Technical Terms*, 2nd ed. New York: McGraw-Hill Book Co., p. 1239.
10. HAWLEY, G.G. (ed.). (1971). *The Condensed Chemical Dictionary*, 8th ed. New York: Van Nostrand Reinhold Co., pp. 703, 734–5.
11. NELSON, R.F., and ADAMS, R.N. (1967). Propylene Carbonate: A versatile solvent for electrochemistry and EPR. J. Electroanal. Chem. **13**, 184–7.
12. STEPHENS, B.G., and SUDDETH, H.A. (1967). Extraction of the 1,10-phenanthroline, and 2,4,6,-tripyridyl-sym-triazine complexes of iron (II) into Propylene Carbonate. Anal. Chem. **39**, 1478–80.
13. PLANT, A.F. (ed.). (1982). *Chemcyclopedia*. Washington, D.C.: American Chemical Society, p. 132.
14. SAX, N.I. (1979). *Dangerous Properties of Industrial Materials*, 5th ed. New York: Van Nostrand Reinhold Co., p. 942.
15. STEPHENS, B.G., LOFTIN, J.C., LOONEY, W.C., and WILLIAMS, K.A. (March 1971). Propylene Carbonate extraction of tris(pentan-2,4-dione)-iron (III) from aqueous solution: Application of the spectrophotometric determination of iron. Analyst **96,**, 230–4.
16. TEXACO CHEMICAL CO. (1984). Submission of data by CTFA. Letter dated April 18, 1984, to Ms. Joanne Whelan (CTFA) from Ken Mjos (Technical Service Representative, Texaco) regarding Propylene Carbonate.*
17. INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). (1976). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Propylene Oxide. **11,** 191–99.
18. EASTMAN KODAK CO. (January 1, 1979). *Eastman Organic Chemicals Catalog* No. 50. Catalog and Price List. Rochester, New York, p. 180.
19. SCHNORBUS, R.R., SCHNORBUS, R.R., and PHILLIPS, W.F. (September 11–16, 1966). A new extraction system for residue analyses (author's abstract). Paper presented at the American Chemical Society Meeting.
20. BENOIT, R.L., and MILANOVA, E. (1979). Vapor pressure and calorimetric data for the solution of sulfur dioxide in aprotic solvents. Can. J. Chem. **57**(11), 1319–23.

*Available upon request: Director, Cosmetic Ingredient Review, 1110 Vermont Ave., N.W., Suite 810, Washington, D.C. 20005.

21. SUBACH, D.J., and BELL, M.E.B. (1973). An analytical procedure for the determination of pesticides in food. J. Chem. Educ. **50**(12), 855–56.
22. THORNBUG, W., and BECKMAN, H. (1969). Pesticide residues. Anal. Chem. **41**(5), 140R–151R.
23. CLAUSS, B., and ACKER, L. (1975). On the contamination of milk and milk products with chlorinated hydrocarbons. I. Methods. Z. Lebensm. Unters. Forsch. **159**(2), 79–84.
24. SCHREIBER, H. (1979). Detection and determination of plant protectant residues. II. Lernen Leisten. **6,** 61–3.
25. KRAUSE, R.D., and KRATOCHVIL, B. (1973). Determination of phenols and aromatic amines by direct titration with bromine in propylene carbonate. Anal. Chem. **45,** 844–8.
26. CHANG, K.Y., and FERRELL, B. (December 2, 1975). Fatty alcohol-propylene carbonate-glycol solvent cream vehicle. U.S. Patent No. 3924004. Syntex, Inc.
27. SHASTRI, S., and SHAIKH, Z.I. (April 4, 1977). Propylene Carbonate ointment vehicle. U.S. Patent No. 4017615. Syntex Corp.
28. LABUTINA, T.V., NIKITINA, A.K., IVANOV, V.A., BRYUKHANOVA, L.A., and BEDNOV, A.N. (1978). Selection of the optimal variant for the scheme of carbon dioxide removal from hydrogen-containing gas by propylene carbonate. Prom. Sanit. Ochistka Gazov. **6,** 15–16.
29. MUKHLENOV, I.P., TARAT, E.Y., TUBOLKIN, A.F., IVANOVA, L.N., and MEDER, A.P. (1974). Absorption of acid components from technological and emission gases. Tezisy Dokl. Vses. Nauchno-Tekh. Konf, Tekhnol. Neorg. Veshchestv Miner. Udobr., 9th. **1,** 216–17.
30. CODE OF FEDERAL REGULATIONS. (Revised as of April 1, 1982). Title 21 Part 175.105. Indirect Food Additives: Adhesive Coatings and Components. Subpart B: Substances for Use as Components of Adhesives.
31. FOOD AND DRUG ADMINISTRATION. (December 22, 1981). Cosmetic product formulation data: Ingredient used in each product category. Computer printout. Washington, D.C.
32. FOOD AND DRUG ADMINISTRATION. (January 5, 1982). (a) Frequency of Trade Name Ingredients in the Cosmetic Product File and (b) Frequency of Common, Usual, or Chemical Names in the Cosmetic Product File. Computer printout. Washington, D.C.
33. CODE OF FEDERAL REGULATIONS. (Revised as of April 1, 1982). Title 21 Part 720.4. Voluntary Filing of Cosmetic Product Ingredient and Cosmetic Raw Material Composition Statement. Information Requested About Cosmetic Products.
34. PHARMAKON RESEARCH INTERNATIONAL. (August 29, 1985). Submission of unpublished data by CTFA. Acute oral toxicity study in rats-14 day. Propylene Carbonate. No. J-253.*
35. THOMPSON, W.R. (1947). Use of moving averages and interpolation to estimate median-effective dose. Bacteriol Rev. **11,** 115.
36. WEIL, C.S. (1952). Tables for convenient calculation of median-effective dose and instructions in their use. Biometrics **8,** 249.
37. SMYTH, H.F., CARPENTER, C.P., WEIL, C.S., and PAZZANI, U.C. (1954). Range-finding toxicity data: List V. Arch. Ind. Hyg. **10,** 61–8.
38. HODGE, H.C., and STERNER, J.H. (1949). Tabulation of toxicity classes. Am. Indust. Hyg. A. Quart. **10,** 93–6.
39. JEFFERSON CHEMICAL COMPANY, INC. (No date). Submission of unpublished data by CTFA. Summary Sheet titled: Propylene Carbonate: Toxicity and Safety.*
40. CODE OF FEDERAL REGULATIONS. (Revised as of April 1, 1982). Title 16 Parts 1500.3 (Definitions), 1500.40 (Method of testing toxic substances), 1500.41 (Method of testing primary irritation substances), 1500.42 (Test for eye irritants).
41. BIOSEARCH, INC. (1983). Submission of unpublished data by CTFA. Summary results of acute toxicity studies. Underarm stick formula containing 20 percent Propylene Carbonate. Code No. 2-24-11.*
42. CTFA. (September 8, 1978). Submission of unpublished data by CTFA. Acute oral, dermal and ocular testing of BB-006, Lot 344-06A. Cream blush containing 2.0 percent Propylene Carbonate. Code No. 2-24-2.*
43. CTFA. (April 1977). Submission of unpublished data by CTFA. CIR safety data test summary response form. Acute oral toxicity of an antiperspirant containing 2.0 percent Propylene Carbonate. Code No. 2-24-4.*
44. CTFA. (November 15, 1979). Submission of unpublished data by CTFA. CIR safety data test summary response form. Lip slicker containing Propylene Carbonate. Acute oral toxicity. Company test code CSE 152.*
45. CTFA. (November 27, 1979). Submission of unpublished data by CTFA. CIR safety data test summary response form. Lip slicker containing Propylene Carbonate. Acute oral toxicity. Company test code CSE 155.*
46. CTFA. (January 26, 1982). Submission of unpublished data by CTFA. CIR safety data test summary response form. Lip gloss containing Propylene Carbonate. Acute oral toxicity. Company test code CSE 153.*

47. DRAIZE, J.H., WOODARD, G., and CALVERY, H.O. (1944). Methods for study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exp. Ther. **82,** 377–90.
48. PHARMAKON RESEARCH INTERNATIONAL. (August 29, 1985). Submission of unpublished data by CTFA. Acute eye irritation test in rabbits. Propylene Carbonate. No. J-254.*
49. KURAMOTO, M., KIMURA, A., ISHIMURA, Y., HAMAMOTO, T., LU, W., TSEN, T., IZUHARA, K., and TSUDA, H. (1972). Acute subcutaneous toxicity and subacute dermal toxicity studies of hexanetriol and propylene carbonate. (English abstract.) Shikoku Igaku Zasshi **28**(2), 276–83.
50. CARPENTER, C.P., and SMYTH, H.F., Jr. (1946). Chemical burns of the rabbit cornea. Am. J. Ophthalmol. **29,** 1363.
51. JOURNAL OFFICIEL DE LA REPUBLIQUE FRANCAISE. (April 21, 1971). Edition Lois et Decrets. Annexe 1: Methode Officielle pour la Determination de L'indice D'irritation Primaire. Annexe 2: Methode Officielle pour la Determination de L'irritation Occulaire. Annexe 3: Methode Officielle pour la L'appreciation de L'aggresivite superficielle Cutanee par Applications Interatives, pp. 3862–4.
52. JOURNAL OFFICIEL DE LA REPUBLIQUE FRANCAISE. (May 6, 1973). Editions Documents Administratifs.
53. KAY, J.H., and CALANDRA, J.C. (1962). Interpretation of eye irritation tests. J. Soc. Cos. Chem. **13**(6), 281–9.
54. GUILLOT, J.P., GIAUFFRET, J.Y., MARTINI, M.C., GONNET, J.F., and SOULE, G. (September 1980). Safety evaluation of cosmetic raw materials: Results obtained with 160 samples from various origins. Fascicle presented at 11th international I.F.S.C.C. Congress in Venice. Author address (Guillot, J.P.): Institut Francais de Recherches et Essais Biologiques, Centre de Lyon/Les Oncins, 69210 L'Arbresle.
55. GUILLOT, J.P., GIAUFFRET, J.Y., MARTINI, M.C., GONNET, J.F., and SOULE, G. (1982). Safety evaluation of gums and thickeners used in cosmetic formulations. Int. J. Cosmet. Sci. **4**(2), 53–65.
56. CTFA. (November 9, 1979). Submission of unpublished data by CTFA. CIR safety data test summary response form. Lip slicker containing Propylene Carbonate. Rabbit eye irritation. Company test code CSE 152.*
57. CTFA. (November 9, 1979). Submission of unpublished data by CTFA. CIR safety data test summary response form. Lip slicker containing Propylene Carbonate. Rabbit eye irritation. Company test code CSE 155.*
58. CTFA. (January 8, 1982). Submission of unpublished data by CTFA. CIR safety data test summary response form. Lip gloss containing Propylene Carbonate. Rabbit eye irritation. Company test code CSE 153.*
59. CTFA. (June 13, 1980). Submission of unpublished data by CTFA. CIR safety data test summary response form. Eye liner containing Propylene Carbonate. Rabbit eye irritation. Company test code CSE 154.*
60 DRAIZE, J.H. (1959). Dermal Toxicity. In: *Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics.* Austin, Texas: The Assoc. of Food and Drug Officials of the U.S. Business Office, Bureau of Foods and Drugs, Food and Drug Administration, pp. 46–59.
61. CTFA. (August 1977). Submission of unpublished data by CTFA. CIR safety data test summary response form. Ophthalmic irritation of an antiperspirant containing 1.67 percent Propylene Carbonate. Code No. 2-24-6.*
62. CTFA. (April 1979). Submission of unpublished data by CTFA. CIR safety data test summary response form. Ophthalmic irritation of an antiperspirant containing 2.0 percent Propylene Carbonate. Code No. 2-24-7.*
63. HEM, S.L., BRIGHT, D.R., BANKER, G.S., and POGUE, J.P. (1974/1975). Tissue irritation evaluation of potential parenteral vehicles. Drug Dev. Commum. **1**(5), 471–7.
64. PHARMAKON RESEARCH INTERNATIONAL. (August 14, 1985). Submission of unpublished data by CTFA. Primary dermal irritation study in rabbits. Propylene Carbonate. No. J-254.*
65. CTFA. (April 1977). Submission of unpublished data by CTFA. CIR safety data test summary response form. Acute dermal toxicity of an antiperspirant containing 2.0 percent Propylene Carbonate. Code No. 2-24-9.*
66. CTFA. (April 1977). Submission of unpublished data by CTFA. CIR safety data test summary response form. Primary skin irritation test on an antiperspirant containing 2.0 percent Propylene Carbonate. Code No. 2-24-5.*
67. CTFA. (August 1977). Submission of unpublished data by CTFA. CIR safety data test summary response form. Primary skin irritation test on an antiperspirant containing 1.67 percent Propylene Carbonate. Code No. 2-24-8.*
68. CTFA. (November 28, 1979). Submission of unpublished data by CTFA. CIR safety data test summary response form. Lip Slicker containing Propylene Carbonate. Rabbit skin irritation. Company test code CSE 152.*
69. CTFA. (January 8, 1982). Submission of unpublished data by CTFA. CIR safety data test summary response form. Lip gloss containing Propylene Carbonate. Rabbit skin irritation. Company test code CSE 153.*

70. PHARMAKON RESEARCH INTERNATIONAL. (September 24, 1985). Submission of unpublished data by CTFA. Acute dermal toxicity test in rabbits. Propylene Carbonate. N. J-253.*
71. PHARMAKON RESEARCH INTERNATIONAL. (September 30, 1985). Submission of unpublished data by CTFA. *Salmonella*/microsome liquid preincubation assay. Propylene Carbonate. No. J-255.*
72. PHARMAKON RESEARCH INTERNATIONAL. (August 23, 1985). Submission of unpublished data by CTFA. Rat hepatocyte primary culture/DNA repair test. Propylene Carbonate. No. J-256.*
73. FROSCH, P.J., and KLIGMAN, A.M. (1977). The Chamber-scarification test for assessing irritancy of topically applied substances. In: *Cutaneous Toxicity.* V.A. Drill and P. Lazar (eds.). New York: Academic Press, pp. 127–154.
74. FOOD and DRUG RESEARCH LABORATORIES. (April 26, 1972). Submission of unpublished data by CTFA. Evaluation of dermal effects. Repeated Insult Patch Test. Five percent by weight Propylene Carbonate in water. I.B.L. No. 10831.*
75. FOOD and DRUG RESEARCH LABORATORIES. (April 26, 1972). Submission of unpublished data by CTFA. Repeated Insult Patch Test. Ten percent by weight Propylene Carbonate in water. I.B.L. No. 10832.*
76. FOOD and DRUG HUMAN CLINICAL LABS, INC. (1983). Submission of unpublished data by CTFA. Final Report: Cumulative Irritancy Assay on 10 Test Materials. Underarm stick formula containing 20 percent Propylene Carbonate. Code No. 2-24-12.*
77. TKL RESEARCH, INC. (1983). Submission of unpublished data by CTFA. Repeated Insult Patch Test. Underarm stick formula containing 20 percent Propylene Carbonate. Code No. 2-24-13.*
78. FOOD and DRUG RESEARCH LABORATORIES. (April 18, 1975). Submission of unpublished data by CTFA. RIPT. Bentone Gel CAO. OE No. 1809.*
79. FOOD and DRUG RESEARCH LABORATORIES. (February 6, 1976). Submission of unpublished data by CTFA. Clinical Safety Evaluation of Bentone Gel-Lantrol. RIPT.*
80. FOOD and DRUG RESEARCH LABORATORIES. (No date). Submission of unpublished data by CTFA. RIPT. Bentone Gel IPM and Bentone Gel MIO. OE No. 1801.*
81. LEO WINTER ASSOCIATES. (March 12, 1979). Submission of unpublished data by CTFA. Repeated insult patch testing of a cream blush containing 2.0 percent Propylene Carbonate. Code No. 2-24-3.*
82. HILL TOP RESEARCH. (May 1977). Submission of unpublished data by CTFA. Repeated insult patch test of two lotion samples on abraded and intact skin (antiperspirant containing 2.0 percent Propylene Carbonate). Code No. 2-24-10.*
83. CTFA. (May 5, 1980). Submission of unpublished data by CTFA. CIR safety data test summary response form. Lip slicker containing Propylene Carbonate. RIPT. Company test code CSE 152.*
84. CTFA. (January 26, 1981). Submission of unpublished data by CTFA. CIR safety data test summary response form. Eye liner containing Propylene Carbonate. RIPT. Company test code CSE 154.*
85. SCHWARTZ, L., and PECK, S.M. (1944). Patch test and contact dermatitis. Pub. Health Rep. **59,** 546–57.
86. WILKINSON, D.S., FREGERT, S., MAGNUSSON, B., BANDMANN, J., CALNAN, C.D., CRONIN, E., HJORTH, N., MAIBACH, H.J., MALTEN, K.E., MENEGHINI, C.L., and PIRILLA, V. (1970). Terminology of contact dermatitis. Acta Dermatovener (Stockholm) **50,** 287–92.
87. CTFA. (No date). Submission of unpublished data by CTFA. CIR safety data test summary response form. Prophetic patch test (Schwartz and Peck) and repeat insult patch test (Shelanski and Shelanski) on eye area products containing 1.51 to 1.98 percent Propylene Carbonate. Code No. 2-24-11.*
88. SHELANSKI, H.A., and SHELANSKI, M.V. (May 1953). A new technique of human patch tests. Proc. Sci. Sec. Toilet Goods Assoc. **19,** 47–9.
89. TKL RESEARCH, INC. (1983). Submission of unpublished data by CTFA. Phototoxicity test. Underarm stick formula containing 20 percent Propylene Carbonate. Code No. 2-24-15.*
90. TKL RESEARCH, INC. (1983). Submission of unpublished data by CTFA. Photoallergy Patch Test. Underarm stick formula containing 20 percent Propylene Carbonate. Code No. 2-24-14.*

but the Panel did consider updated information regarding uses and use concentrations. The Panel determined to not reopen the safety assessment.

Phenyl Trimethicone uses have increased from 169 in 1981 to 279 in 2002, based on industry voluntary reports provided to FDA (Elder 1986; FDA 2002). An industry survey in 2003 indicated that use concentrations range from 0.0075% to 36% (CTFA 2004). The maximum value in that range is higher than the maximum use concentration of 5% reported in 1981 (Elder 1986). Table 17 presents the available use and concentration information for Phenyltrimethicone. The most recent information now represents the present practice of use and concentration.

The Panel considered the increased use concentrations in the context of the reproductive and developmental toxicity data in the original safety assessment. Phenyl Trimethicone was not teratogenic at 500 mg/kg/day in rats and rabbits. For a 70-kg person, this dose corresponds to 35 g/day. At the current maximum use in lipsticks and the amount of lipstick used in a typical day, a dose of Phenyl Trimethicone was estimated to be 10 mg/day. This dose was 3500× lower than the observable effect level.

REFERENCES

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2004. Concentration of use—phenyl trimethicone. Unpublished data submitted by CTFA on May 10, 2004. (2 pages).[18]

Elder, R. L. 1986. Final report on the safety assessment of Phenyl Trimethicone. *J. Am. Coll. Toxicol.* 5:353–371.

Food and Drug Administration (FDA). 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

PROPYLENE CARBONATE

A safety assessment of Propylene Carbonate was published in 1987 with the conclusion that it is safe as a cosmetic ingredient in the present practices of use and concentration (Elder 1987). Studies published since the last assessment were reviewed along with updated information concerning frequency of use and use concentrations. The CIR Expert Panel determined to not reopen the safety assessment.

Based on voluntary reports provided by industry to FDA, there were 295 reported uses in 1981 (Elder 1987) and 178 reported uses in 2002 (FDA 2002). Use concentrations from an industry survey (CTFA 2003) ranged from 0.003% to 6%, not very different from the use concentration range reported in 1981 of ≤0.1% to >5% (Elder 1987).

Table 18 presents the available use and concentration information for Propylene Carbonate. The most recent information constitutes present practices of use and concentration.

[18]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

REFERENCES

Barry, B. W., S. M. Harrison, and P. H. Dugard. 1985. Vapour and liquid diffusion of model penetrants through human skin; correlation with thermodynamic activity. *J. Pharm. Pharmacol.* 37:226–236.

Bushy Run Research Center. 1989. Propylene Carbonate: Nine-Day Aerosol Inhalation Study on Rats. Unpublished data. Project Report 51–633.[19]

Bushy Run Research Center. 1990. Chronic Dermal Oncogenicity Studies in C3H/HeJ Mice. Unpublished data. Project Report 52–527.[19]

Bushy Run Research Center. 1991. Propylene Carbonate: Fourteen-Week Aerosol Inhalation Study on Rats with Neurotoxicity Evaluation. Unpublished data. Project Report 52–637.[19]

Central Toxicology Laboratory. 2001. Jeffsol Propylene Carbonate-NF: Eye Irritation Study in Rabbits. Unpublished data. Report CTL/FB5863/REG/REPT.[19]

Chemische Werke Huls Ag. 1979. Mutagenitatsontersuchung von Propylencarbonat mit Hilfe des *Salmonella typhimurium*/ Mirosoman-Mutagentats-Tests nach Ames. Unpublished data. Report 41.[19]

Elder, R. L., ed. 1987. Final Report on the Safety Assessment of Propylene Carbonate. *J. Am. Coll. Toxicol.* 6(1):23–51.

Gottschalck, T. E., and G. N. McEwen, Jr., eds. 2004. *International Cosmetic Ingredient Dictionary and Handbook*, 10th ed., Vol. 2. Washington, DC: CTFA.

Kawanami, H., A. Sasaki, K. Matsui, and Y. Ikushima. 2003. A rapid and effective synthesis of propylene carbonate using a supercritical CO_2-ionic liquid system. *Chem. Commun.* 7:896–897.

Muzikar, J., T. Van de Goor, B. Gas, and E. Kenndler. 2001. Extension of the application range of UV-absorbing organic solvents in capillary electrophoresis by the use of contactless conductivity detector. *J. Chromatogr. A* 924:147–154.

Papciak, R. J., and V. T. Mallory. 1990. Acute Toxicological evaluation of propylene carbonate. *Acute Toxicity Data* 1:15–16.

Pharmakon Research International, Inc. 1986. Acute Dermal Toxicity Study in Rabbits. Unpublished data. Report PH 422-TX-006-86.[19]

Pharmakon Research International, Inc. 1986. Micronucleus Test OECD. Unpublished data. Report PH 309-TX-004-85.

Pharmakon Research International, Inc. 1988. Developmental Toxicity Study in Rats. Unpublished data. Report PH 328-TX-001-88.[19]

Pharmakon Research International, Inc. 1988. Dose-Range-Finding Developmental Toxicity Study in Rats. Unpublished data. Report PH-32DR-TX-001-87.[19]

Pharmakon Research Interantional, Inc. 1988. Dose-Range-Finding 28-Day Oral Toxicity Study in Rats. Unpublished data. Report PH-436-TX-001-87.[19]

Pharmakon Research International, Inc. 1989. Subchronic 90 Day Oral Toxicity Study in Rats. Unpublished data. Report PH-470-TX-001-88.[19]

Sutou, S. 1996. Achievements by CSGMT MMS: The collaborative study group fo rthe micronucleus test in mammalian Mutagenesis Study Group for the Environmental Mutagen Society of Japan. *Mutat. Res.* 340:151–174.

Ursin, C., C. M. Hansen, J. W. Van Dyk, P. O. Jensen, I. J. Christensen, and J. Ebbehoej. 1995. Permeability of comericial solvents through living human skin. *Am. Ind. Hyg. Assoc. J.* 56:651–660.

Yamada, Y., M. Nakahara, M. Kohno, M. Otsuka, and O. Takaiti. 1989. Metabolic fate of the new anti-ulcer drug enprostil in animals. 4th communication: Effect on hepatic drug metabolizing enzyme system in rats. *Arzneimittelforschung* 39:356–360.

POLYVINYLPYRROLIDONE/VINYL ACETATE COPOLYMER

In 1983, the CIR Expert Panel concluded that this ingredient is safe as a cosmetic ingredient under the present practices of product and concentration use (Elder 1983). New studies available since that review have been considered by the Expert Panel,

[19]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

TABLE 18
Current and historical uses and concentrations of Propylene Carbonate in cosmetics

Product category	1981 uses (Elder 1984)	2002 uses (FDA 2002)	1981 concentrations (Elder 1984) %	2003 concentrations (CTFA 2003) %
Bath				
Oils, tablets and salts	1	1	>1–5	—
Eye makeup				
Eyebrow pencils	6	6	>1–5	0.3
Eyeliners	17	15	>1–5	0.2–0.6
Eye shadow	42	10	>0.1–5	0.4–1
Eye lotions	1	—	>1–5	—
Eye makeup remover	—	3	—	—
Mascara	34	22	>0.1–5	2–4
Other eye makeup	9	12	>0.1–5	0.5
Fragrances				
Colognes and toilet waters	5	—	>1–5	—
Perfumes	4	—	>1–5	—
Noncoloring hair care				
Conditioners	1	—	>1–5	—
Tonics, dressings, etc.	—	1	—	—
Hair Coloring				
Other hair coloring	3	1	>1–5	—
Makeup				
Blushers	13	1	≤0.1–>5	1–2
Face powders	1	—	>1–5	0.4
Foundations	11	3	>0.1–5	0.6–2
Rouges	—	—	—	0.1
Lipsticks	95	35	≤0.1–>5	0.03–2
Makeup bases	13	4	>0.1–1	—
Makeup fixatives	1	2	>1–5	—
Other makeup	9	20	>0.1–5	1
Nail care				
Creams and lotions	1	—	>1–5	—
Polish and enamel	—	—	—	0.003
Polish and enamel removers	—	6	—	1
Other nail care	—	—	—	4
Personal hygiene				
Underarm deodorants	—	2	—	0.2–5
Other personal hygiene	4	26	≤0.1–>5	—
Skin care				
Cleansing creams, lotions, etc.	9	1	>1–5	0.1
Face and neck skin care	1*	—	>0.1–1*	—
Body and hand skin care		—		—
Moisturizers	2	4	>1–5	0.02–0.2
Night skin care	4	1	>1–5	—
Paste masks/mud packs	—	1	—	0.3–2
Skin fresheners	1	—	>0.1–1	—
Suntan preparations				
Suntan gels, creams, and liquids	6	1	>1–5	0.08–0.2
Other suntan preparations	1	—	>1–5	—
Total uses/ranges for Propylene Carbonate	**295**	**178**	**≤0.1–>5**	**0.003–5**

*These categories were combined originally, but are now separate.