Amended Safety Assessment of Propylene Carbonate as Used in Cosmetics

Status:	Draft Amended Report for Panel Review
Release Date:	September 6, 2024
Panel Meeting Date:	September 30 – October 1, 2024

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

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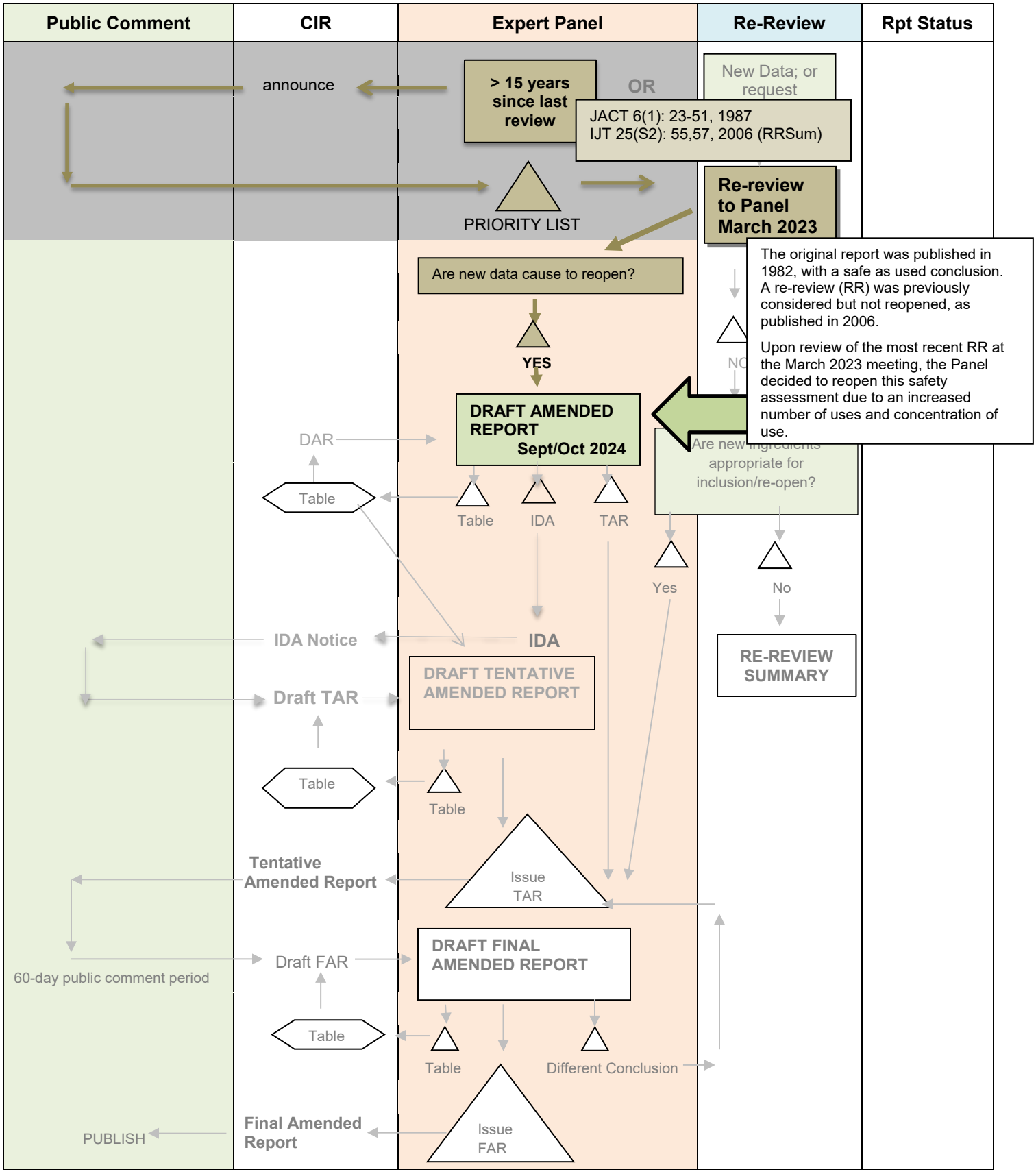
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Propylene Carbonate

MEETING September/October 2024



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR
Date: September 6, 2024
Subject: Amended Safety Assessment of Propylene Carbonate as Used in Cosmetics

Enclosed is the Draft Amended Report on the Safety Assessment of Propylene Carbonate as Used in Cosmetics. (It is identified as *report_PropyleneCarbonate_092024* in the pdf document). In 1987, the Panel published a safety assessment on Propylene Carbonate with the conclusion that Propylene Carbonate is safe as a cosmetic ingredient in the present practices of use and concentration, as stated in that report (*originalreport_PropyleneCarbonate_092024*). The Panel previously considered a re-review of this ingredient in 2004 (*2004RRdata_PropyleneCarbonate_092024*) and re-affirmed the 1987 conclusion, as published in 2006 (*rereview2006_PropyleneCarbonate_092024*). Since it had been at least 15 years since the previous re-review, the Panel again considered a re-review of this ingredient in March 2023, and determined to re-open the report due to increased frequency and concentration of use.

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%.

Unpublished data have been received and incorporated into this report. These data include:

- Human patch test, 5-d clinical use assay, and clinical use test on serum containing 17.84% Propylene Carbonate (*data1_PropyleneCarbonate_092024*)
- Maximization assay in human skin using product containing 17.84% Propylene Carbonate (*data2_PropyleneCarbonate_092024*)

Additional supporting documents for this report package include a flow chart (*flow_PropyleneCarbonate_092024*), report history (*history_PropyleneCarbonate_092024*), a search strategy (*search_PropyleneCarbonate_092024*), a data profile (*dataprofile_PropyleneCarbonate_092024*), minutes from which the original report and re-review were discussed (*originalminutes_PropyleneCarbonate_092024*), and transcripts from recent meetings at which Propylene Carbonate was discussed (*transcripts_PropyleneCarbonate_092024*).

If no further data are needed, the Panel should formulate an updated Discussion and issue a Tentative Amended Report. However, if additional data are required, the Panel should be prepared to identify those needs and issue an Insufficient Data Announcement.

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

Propylene Carbonate Data Profile* – September 2024 – Writer, Priya Cherian																														
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{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	XO	XO	X	O	X	X		X	XO	X	X			XO	XO			XO	O	X	XC		

* "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 – 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.

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.

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ABBREVIATIONS

ADME	absorption, distribution, metabolism, excretion
CIR	Cosmetic Ingredient Review
CLP	classification, labeling, and packaging
CMC	carboxymethylcellulose
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
Dictionary	web-based *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
GHS	globally harmonized system
HET-CAM	hen's egg chorioallantoic membrane
LD_{50}	median lethal dose
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect-level
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
SIOPT	single-insult occlusive patch test
TCA	trichloroacetic acid
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program

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 Expert Panel for Cosmetic Ingredient Safety (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, as stated in that report. The Panel first considered a re-review of this report in September 2004, and the Panel 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, 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 an 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 August 2024 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/).

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[5] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definition and Structure

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]

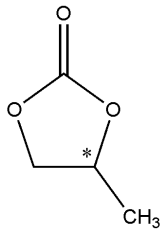

Figure 1. Propylene Carbonate

Propylene Carbonate is a polar aprotic substance with similar characteristics to other organic solvents such as acetonitrile and acetone.[6] 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. 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.[5]

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 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.[7] However, Propylene Carbonate has also been reported to be synthesized via the phosgenation of propylene glycol, 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]

USE

Cosmetic

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics and does not cover its use in airbrush delivery systems. Data included herein were obtained from the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) in 2023 and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data were provided by cosmetic product categories, based at that time on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2023 VCRP survey data, Propylene Carbonate is reported to be used in 882 formulations (874 leave-on formulations and 8 rinse-off formulations; Table 2).[8] 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)).[9] In 2002/2003, this ingredient was reported to be used in 178 formulations, at up to 5% (in underarm deodorants).[3]

It should be noted that Propylene Carbonate is used in baby products (concentration not reported) and products used near the eyes (e.g., in eyeliner at up to 2.7%). In addition, Propylene Carbonate may be used 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 at up to 1.4%, and face powders 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.

Although products containing this ingredient may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients (and without consumer habits and practices data or particle size data related to this use technology), 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.[10]

Non-Cosmetic

Propylene Carbonate is used as 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 also 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.[11] Propylene Carbonate is also permitted for use as an adhesive in articles 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).[12] Water [3H] 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 detector 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 (ADME)

In Vitro

The in vitro degradation rate of Propylene Carbonate (1 mmol) in the blood of Wistar rats was evaluated.[5] 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 (hydrolyzation 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

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 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.

Propylene Carbonate was not lethal to 6 rats exposed to concentrated vapors for 8 h.[2] 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 (animals treated with up to 20 ml/kg Propylene Carbonate).

Dermal

An acute dermal toxicity assay was performed according to Organisation for Economic Co-operation and Development Test Guidelines (OECD TG) 402.[5] 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

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.[5] 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

Rats (6/sex/group; strain not stated) were exposed to Propylene Carbonate vapor for 8 h and observed for 7 d.[5] No other details were provided for this study. No signs of toxicity were observed.

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)).[5] 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 to the eyes, mucous membranes, and nasal cavities were observed in a 9-d inhalation toxicity 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^2 air was also established in this assay due to localized signs of toxicity (i.e., periocular swelling).

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 6-16.[5] 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).[5] 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.[5] The test substance was determined to be non-genotoxic.

In Vivo

A mammalian erythrocyte micronucleus test was performed according to OECD TG 474.[5] 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).[5] Animals of the test substance group were sacrificed at 30, 48, and 72 h, and bone marrow was evaluated. Propylene Carbonate was considered to be non-genotoxic. Controls gave expected results.

CARCINOGENICITY STUDIES

Dermal

The potential carcinogenicity of Propylene Carbonate (50 µl; tested neat) was evaluated in mice (strain, number, and sex of animals not stated).[5] Animals were administered the test substance via the dorsal skin, 2x/wk, for 104 wk (level of occlusion not stated). No treatment-area skin tumors were observed. No other details regarding this study were provided.

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 moderately irritating 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).[5] 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.[13] 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.[14,15] 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 considered to be non-sensitizing in a maximization assay performed in 26 subjects.[16]

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.[17] 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.[5] 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 as stated in that report. This conclusion was reconsidered at the September 2004 Panel meeting and the conclusion was re-affirmed, as published in 2006. In 2023, the Panel determined that this safety assessment should be for re-evaluation due to an increase in frequency and concentration of use.

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%.

The permeability constant of Propylene Carbonate was determined to be 0.2 g/m^2h 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 29.1 ml/kg undilute 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 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.

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. A statistically significant reduction in the fetuses exhibiting incomplete ossification of the 3rd sternebrae was observed in the low- and mid-dose group when compared to controls in a developmental and reproductive toxicity assay performed in rats treated with undiluted Propylene Carbonate (up to 5000 mg/kg/d) via gavage on gestation days 6-15. However, this effect was not determined to be of toxicological importance, according to study authors. No other abnormalities were observed in fetuses. Adverse effects were observed in treated maternal animals (e.g., death, post-dose salivation, cyanosis).

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 considered to be 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.

PREVIOUS DISCUSSIONS

Discussion from Original Report Published in 1987

Propylene Carbonate is generally used in cosmetics at concentrations ranging from ≤ 0.1 to 5.0%. Clinical studies indicated that Propylene Carbonate concentration of 5 and 10% in aqueous solutions were non-irritating and non-sensitizing. Undiluted Propylene Carbonate was moderately irritating. In several instances throughout the safety review, reference was made 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.

Discussion from Re-Review Summary Published in 2006

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. Studies published since the last assessment were reviewed along with updated information concerning frequency of use and use concentrations. The CIR Expert Panel determined not to reopen the safety assessment.

DISCUSSION

To be determined.

CONCLUSION

To be determined.

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	5
Boiling Point (ºC)	241.6	18
Water Solubility (g/l @ 25ºC & pH 7)	200	5
log K_{ow} (@ 20ºC)	-0.41 (estimated)	5
Disassociation constants (pKa @ 20ºC)	3.92	5

Table 2. Frequency (2023/2002) and concentration (2022/2003) of use of Propylene Carbonate according to likely duration and exposure and by product category

	# of Uses		*Max Conc of Use (%)*	
	2023[8]	**2002**[3]	**2022**[9]	**2003**[3]
Totals	**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				
Baby Lotions/Oils/Powders/Creams	2	NR	NR	NR
Other Baby Products	1	NR	NR	NR
Bath Preparations (diluted for use)				
Bath Oils, Tablets, and Salts	NR	1	NR	NR
Eye Makeup Preparations				
Eyebrow Pencil	15	6	0.08 – 0.36	0.3
Eyeliner	58	15	0.14 – 2.7	0.2 – 0.6
Eye Shadow	47	10	0.01 – 0.7	0.4 – 1
Eye Lotion	3	NR	NR	NR
Eye Makeup Remover	4	3	NR	NR
Mascara	44	22	0.75 – 2.2	2 – 4
Other Eye Makeup Preparations	33	12	0.34	0.5
Hair Preparations (non-coloring)				
Shampoos (non-coloring)	NR	NR	0.24	NR
Tonics, Dressings, and Other Hair Grooming Aids	1	1	NR	NR
Other Hair Preparations	1	NR	NR	NR
Hair Coloring Preparations				
Hair Tints	NR	NR	NR	NR
Other Hair Coloring Preparation	NR	1	NR	NR
Makeup Preparations				
Blushers (all types)	16	1	0.04 – 0.76	1 – 2
Face Powders	7	NR	1.4	0.4
Foundations	60	3	0.16 – 0.45	0.6 – 2

Table 2. Frequency (2023/2002) and concentration (2022/2003) of use of Propylene Carbonate according to likely duration and exposure and by product category

	# of Uses		*Max Conc of Use (%)*	
	2023[8]	**2002**[3]	**2022**[9]	**2003**[3]
Leg and Body Paints	2	NR	NR	NR
Lipstick	389	35	0.0064 – 3.9	0.03 - 2
Makeup Bases	21	4	0.03 – 0.075	NR
Rouges	1	NR	NR	0.1
Makeup Fixatives	1	2	NR	NR
Other Makeup Preparations	65	20	0.16 – 0.84	1
Manicuring Preparations (Nail)				
Basecoats and Undercoats	2	NR	NR	NR
Cuticle Softeners	NR	NR	0.6	NR
Nail Creams and Lotions	NR	NR	0.15	NR
Nail Polish and Enamel	1	NR	1.1	0.003
Nail Polish and Enamel Removers	NR	6	6	1
Other Manicuring Preparations	2	NR	NR	4
Personal Cleanliness Products				
Deodorants (underarm)	33	2	0.93 – 1.4 (aerosol)	0.2 – 5
Other Personal Cleanliness Products	NR	26	NR	NR
Skin Care Preparations				
Cleansing	4	1	0.78 – 1.7	0.1
Face and Neck (exc shave)	11	NR	3.8 – 6 (not spray)	NR
Body and Hand (exc shave)	13	NR	0.05 (not spray)	NR
Foot Powders and Sprays	NR	NR	0.28	NR
Moisturizing	22	4	0.45 (not spray)	0.02 – 0.2
Night	4	1	17.9 (not spray)	NR
Paste Masks (mud packs)	NR	1	NR	0.3 - 2
Skin Fresheners	1	NR	NR	NR
Other Skin Care Preparations	17	NR	NR	NR
Suntan Preparations				
Suntan Gels, Creams, and Liquids	1	1	0.02 – 0.2 (not spray)	0.08 – 0.2

NR – not reported

*likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

**Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 3. Repeated dose toxicity studies[5]

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 in m high-dose animals include increased bilirubin, albumin, creatinine, chloride; decreased phosphorus, glucose, protein). 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[5]

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. A systemic NOAEC of 1000 mg/m^3 air, a local LOAEC of 500 mg/m^3 air, and a NOAEC of 100 mg/mg^2 air were determined.

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

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	5
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.	13

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 control article The majority of users described products as either very or somewhat gentle; the 4 individuals who experience discomfort rated the product as somewhat or very irritating The evaluating dermatologist did not observe any visible clinical irritation throughout the study.	14
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.	15
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	16

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	17
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	5
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)	5
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	5
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	5

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

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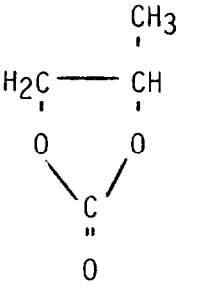
Final Report on the Safety Assessment of Propylene Carbonate

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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COSMETIC INGREDIENT REVIEW

C I R

Memo

To: CIR Expert Panel

From: Dina M. Benes

Date: September 9, 2004

Subject: Re-review of Propylene Carbonate

In 1987 CIR Expert Panel issued a Final Report for Propylene Carbonate with the conclusion stating:

> "Propylene Carbonate is safe as a cosmetic ingredient used in the present practices of use and concentration."

Current use and concentration data are provided. Uses have decreased. New published studies were found and have been summarized. We expect to receive new unpublished data from industry and will provide those data in a separate mailing.

Attached is the original 1987 report. The Panel should determine if the original conclusion is still valid in light of the new data. If it is not, the Panel should reopen this safety assessment. If the conclusion is still valid, then the panel can decide to not reopen this report.

Re-review of Propylene Carbonate

INTRODUCTION

A safety assessment of Propylene Carbonate (CAS # 108-32-7) was published in 1987 with the conclusion that it is "safe as a cosmetic ingredient used in the present practices of use and concentration."(CIR, 1987).

Propylene carbonate functions as a solvent and a viscosity decreasing agent (Gottschalck & McEwen, 2004).

USE

Table 1 presents the current and historical frequencies and concentrations of use for Propylene Carbonate.

Table 1. 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 Preparations				
Oils, tablets and salts(143)	1	1	>1-5	-
Eye Makeup Preparations				
Eyebrow pencils(102)	6	6	>1-5	0.3
Eyeliners(548)	17	15	>1-5	0 2-0 6
Eye shadow(576)	42	10	>0.1-5	0.4-1
Eye lotions(25)	1	-	>1-5	-
Eye makeup remover(100)	-	3	-	-
Mascara(195)	34	22	>0.1-5	2-4
Other eye makeup preparations(152)	9	12	>0 1-5	0.5
Fragrance Preparations				
Colognes and toilet waters(684)	5	-	>1-5	-
Perfumes(235)	4	-	>1-5	-
Non-coloring Hair Preparations				
Hair conditioners(651)	1	-	>1-5	-
Hair tonics, dressings, etc (598)	-	1	-	-
Hair Coloring Preparations				
Other hair coloring preparations(55)	3	1	>1-5	-
Makeup Preparations				
Blushers(245)	13	1	≤0.1- >5	1-2
Face powders(305)	1	-	>1-5	0 4
Foundations(324)	11	3	>0 1-5	0 6-2
Rouges(28)	-	-	-	0 1
Lipsticks(962)	95	35	≤0.1- >5	0 03-2
Makeup bases(141)	13	4	>0 1-1	-
Makeup fixatives(20)	1	2	>1-5	-

Table 1 (continued). 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)
Other makeup preparations(201)	9	20	>0.1-5	1
Nail Care Products				
Creams and lotions(15)	1	-	>1-5	-
Polish and enamel(123)	-	-	-	0.003
Polish and enamel removers(36)	-	6	-	1
Other(55)	-	-	-	4
Personal Hygiene Products				
Underarm deodorants(247)	-	2	-	0.2-5
Other personal hygiene products(308)	4	26	≤0.1->5	-
Skin Care Preparations				
Skin cleansing creams, lotions, liquids, and pads(775)	9	1	>1-5	0.1
Face and neck skin care preparations(310)	1*	-	>0.1-1*	0.02-6
Body and hand skin care preparations(840)				
Moisturizers(905)	2	4	>1-5	0.02-0.2
Night skin care preparations(200)	4	1	>1-5	-
Paste masks (mud packs)(271)	-	1	-	0.3-2
Skin fresheners(184)	1	-	>0.1-1	-
Suntan Preparations				
Suntan gels, creams and liquids(131)	6	1	>1-5	0.08-0.2
Other suntan preparations(38)	1	-	>1-5	-
Total uses/ranges for Propylene Carbonate	**295**	**178**	**≤0.1->5**	

*This category was combined when the original safety assessment was performed and is now two separate categories.

NEW DATA

CHEMISTRY

In a recent study, Kawanami et al. (2003) states that propylene carbonate is synthesized from propylene oxide and carbon dioxide under supercritical conditions. It was achieved in nearly 100% yield and 100% selectivity within 5 minutes. The time that it used to take to achieve this in the presence of their catalysts was reported to be more than 6 hours at very high temperatures. The new method for production involves a promotion of CO_2 chemical fixation in supercritical CO_2, especially at the near-critical pressure in the presence of a small amount of DMF even without catalysts. The DMF functions as a $scCO_2$ soluble acid-base catalyst. To improve the activity and selectivity further, $scCO_2$-ionic liquid biphasic system was applied to the CO_2 fixation because it can be also used as a prominent acid-base catalyst as well as a suitable reaction media.

METABOLIC EFFECTS

Yamada et al. (1989) reported a study that tested the metabolic fate of the new anti-ulcer drug, Enprostil, in Sprague- Dawley male rats. The solvent used in the drug was propylene carbonate, which was also used for the control group in the experiment. 20 µg/kg/ 5ml of Enprostil and 5 ml/kg of propylene carbonate were administered orally once daily for either 1 day, 7 days, or 14 days according to the different groups. The rats were weighed before each administration, fasted for 24 hours after the last dose of the drug or for 24 hours before liver excision, and then killed by cutting the carotid artery. The livers were excised, weighed, and then hepatic microsomal fractions were prepared.

In the rats that were given multiple doses of Enprostil or propylene carbonate tended to have a lower body weight gain as opposed to the untreated control group. However, it was found that these differences did not seem significant at any time. Compared to the propylene carbonate treated group and untreated control group, the enprostil treated group had slightly, but significantly lower cyt. b_5 content. In both of the treated groups, there was a slight but significant increase (20%) in microsomal protein as compared to the untreated control group that were given administrations for 14 days. It was concluded that both the Enprostil and propylene carbonate had little effect on any drug metabolizing enzyme inducing or inhibiting activity in rats.

UV ABSORPTION

Muzikar et al. (2001) stated that propylene carbonate, among other solvents, generally had high ultra-violet absorbance (specific range not stated). Propylene carbonate was used in a very limited number of applications with severe restrictions concerning the choice of analytes because it has a optical cut-off around 230-260 nm , which makes it unsuitable for detection lower than around 240 nm, and leads to high detection noise even at higher wavelengths.

PERMEATION EFFECTS

Barry et al.(1985) evaluated a study that investigated the vapor and liquid permeation through human skin. The model penetrants used were bezyl alcohol, benzaldehyde, aniline, anisole, and 2-phenylethanol, which were appied in model vehicles. Propylene carbonate was used as one of the eight vehicles in this experiment. Human abdominal cadaver skin (0.4 mm thick) was prepared and mounted in glass diffusion cells, and the permeation of each specimen was checked; any highly permeable specimens were rejected. Fresh samples were introduced to the specimens daily for a total of 4 days.

After all graphs were plotted and calculations were made, propylene carbonate did not increase skin permeability. The damage ratio for the control was 1.9 ± 1, and the ratio for propylene carbonate was 1.0 ± 0.5.

Menke & Chelton (1988) described a study in which ethylene glycol dimethyl ether (EGDME) was exposed to gloves to test the permeation of the material. If EGDME was to be absorbed through the gloves, there would be a huge risk for skin exposure. This could be harmful because EGDME has been know to cause reproductive effects in animal studies. Samples were injected into a 1-m Carbowax column in a gas chromatograph that was equipped with a flame ionization detector. The limit of detection of EGDME in the chamber was 1µg EGDME/ cm^3 air. Breakthrough of EGDME was determined to occur when a signal of 10 µg EGDME/cm^3 air was detected. A 31-mil butyl rubber provided protection for only 410 minutes.

It has been known that binary mixtures of solvents change the properties of each component to cause an accelerated permeation and shortened breakthrough times. Since pure EGDME only provided protection for 410 minutes, the concern of a mixture of say propylene carbonate may reduce that even further. A 21-mil butyl rubber was challenged to a mixture of pure EGDME and EGDME/ propylene carbonate. They were tested on separate samples during a 15 day recycling experiment where the patches of rubber were reconditioned by drying either by air, oven, or vacuum. The EGDME/ propylene carbonate mixture was found to increase the breakthrough time. Breakthrough was not detected at the end of any of the 15 challenge periods (8 hours each). The material only required overnight drying at room temperatures. Tests were repeated in which exposure was that of a (normal work shift with the gloves). At 24 hours there was the first sign of breakthrough (only 0.002 µg/µL of EGDME), and by 41 hours the concentration had only risen to 0.014 µg/µL. At this point the experiment was discontinued, and it was concluded that propylene carbonate retarded the permeation of EGDME into the membrane tot he extent that it remained close to the surface where it could evaporate overnight.

Ursin et al. (1995), described a study which focused on the rate of permeation of a solvent through human skin. Living human skin was obtained from a healthy females during plastic surgery of the breast. The samples were thinned by removing the dermal tissue from the epidermis and then stretched to a thickness of 300- 600 µm. Each piece of surgically removed skin usually provided sufficient material to run 9 permeation experiments. The permeability rate of propylene carbonate was determined to be 0.7

g/m^{2}h compared to a permeability rate for water of 24 g/m^{2}h. Therefore, it was concluded that propylene carbonate is not readily absorbed through the skin.

ACUTE TOXICITY

ORAL

Papciak & Mallory (1990) stated that 10 Sprague Dawley rats were administered 5.0 g/kg of propylene carbonate by gavage for 14 days. No animals died during the study, therefore the oral LD_{50} was greater than 5.0 g/kg. No visible lesions were observed at terminal necropsy.

DERMAL

Papciak & Mallory (1990) reported no signs of dermal toxicity when a group of 10 New Zealand White Rabbits received 2.0 g/kg of propylene carbonate. The test material was applied to their shaved backs (about 10% of total body area) for 24 hours over a duration of 14 days. The dermal LD_{50} was greater than 2.0 g/kg, and there was slight erythema at the application site through day 2 but returning to normal by day 3. No visible lesions were observed at terminal necropsy.

DERMAL IRRITATION

Papciak & Mallory (1990) noted that 6 young adult New Zealand White rabbits were exposed to 0.5 ml of propylene carbonate to shaved skin sites. Dermal scoring of erythema and edema on both skin sites at 24 and 72 hours, and calculation of the primary irritation index was according to the Draize scale. The study duration was for 72 hours. The Draize Primary Irritation Index equaled 0.2 of 8.0; considered to be minimally irritating. Well-defined erythema and very slight edema was observed only at the 24 hour observation, and all scores returned to normal within 72 hours.

OCULAR IRRITATION

Papciak & Mallory (1990) stated that 0.1 ml of propylene carbonate was administered directly to one eye of 6 young adult New Zealand White rabbits for 7 days. Ocular scoring of corneal, iridial, and conjuctival lesions with calculation of an ocular irritation score was according to Draize scale. The Draize ocular irritation score was 12.5 of 110 at 1 hour post treatment; considered minimally irritating. Slight ocular irritation was observed through 72 hours, but all scores returned to normal by day 7.

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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.

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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.

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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.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: March 13, 2023

SUBJECT: Propylene Carbonate

Anonymous. 2004. Clinical Evaluation Report: Human Patch Test (serum containing 17.84% Propylene Carbonate).

Anonymous. 2004. 5-Day Facial Use Test (serum containing 17.84% Propylene Carbonate).

Anonymous. 2004. Clinical Use Test (serum containing 17.84% Propylene Carbonate).

Serum contains 17.84% Propylene Carbonate

[redacted]

CLINICAL EVALUATION REPORT: HUMAN PATCH TEST

This test follows the procedure described in SOP, HPT.1 **TO:** [redacted]

PRODUCT PROFILE NO: [redacted] DATE: July 30, 2004 LAB REF.: [redacted]

1. TEST MATERIAL: [redacted] Serum [redacted]

2. CONTROL MATERIAL: [redacted] Serum [redacted]

3. TEST PROCEDURE:

Single-Insult (24hr.)__X__ Occlusive (Blenderm) Patch__X__Semi-Occlusive Patch_____.

4. CONCENTRATION:

Full-Strength__X__ Aqueous ____Solution _____ Dispersion_____ Aqueous Paste_____.
Other:_____.

__X__ Volatiles were allowed to evaporate on the patch __~30 minutes prior to occlusion.__ Patch was hydrated just prior to application to skin _____.

5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS*	*IRRITATION SCORE**									
		0	±	1	1+	2	2+	3	3+	4	PII
[redacted] Serum [redacted]	18	16	2	0	0	0	0	0	0	0	0.06
[redacted] Serum [redacted]	18	18	0	0	0	0	0	0	0	0	0.00

____ Skin staining noted. Erythematous response were read "through" the Stain.

6. CONCLUSIONS:

A. There were no significant differences in irritancy observed between the Test Material (s) and the Reference Control (s). __X__.

B. _____.

Study Conducted By: [redacted] Approved By: [redacted]

* SCORE
0 = No evidence of any effect.
± (Barely Perceptible) = minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2 (Moderate) = Pink-red erythema visibly uniform in entire contact area.
3 (Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema.

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. - Primary Irritation Index - a value depicting the average skin response of the test panel as a whole. It is calculated by choosing the higher of the two Irritation Scores per panelist, adding them all together and dividing by the total number of test subjects.

[redacted]

Profile #[redacted]

MEMORANDUM

To: [redacted]

From: [redacted]

Date: October 06, 2004

Subject: [redacted] Serum [redacted] 5-Day Facial Use Test

Background/Purpose:

[redacted] Serum [redacted] is a product being developed for the Japan market. A 5-Day Facial Use Test was conducted to evaluate the formulation for safety.

Serum contains 17.84% Propylene Carbonate

Conclusion:

[redacted] Serum [redacted] performed marginally and will be further evaluated in a clinical use study.

Test Materials:

Test (T): (Ref. 8967) [redacted] Serum [redacted]
Control (C): (Ref. 8968) [redacted] Serum [redacted]
Rationale: The control was selected because it is a product with a form and function similar to the test product. It has been previously test with acceptable results.

Test Date:

August 30- September 03, 2004

Procedure:

1.ml applied to each side of the face once daily for 5 days•

This study followed the procedure outlined in SOP CUT 5.1 dated 4/12/02 with the following specifications:

-19 female and male panelists completed the study.
-Panelists reported to the lab twice a day for 5 consecutive days.

• On Friday panelists returned at 11:00 AM due to [redacted]. Only 1 application was given due to the compressed time frame of the return visit. Therefore, for this test there were a total of 9 applications

-Following a visual exam, the products were dispensed onto cotton pads, and the panelist washed the designated side of their face.
-Panelists were not permitted to wear facial make-up or use their own moisturizers for the duration of the study.
-The afternoon visit consisted of a visual exam and completion of a subjective discomfort questionnaire.
-On the last visit of the study, panelists completed a questionnaire rating the gentleness of the products.

Results:

Visible Changes

[redacted] Serum [redacted] performed acceptably. There were no visible clinical changes observed. [redacted] Serum [redacted] performed acceptably with regard to visible changes.

Subjective Discomfort

Subjectively, [redacted] Serum [redacted] performed marginally. There were four (4) panelists (GC, SW, MH, and JB) that experienced subjective discomfort. See Table 1 for details.

Subjective Discomfort Table

Table 1

Panelists	Subjective Discomfort	Duration	Gentleness Rating
GC (T only)	Mild burning on the right cheek only	Days 1-5 that lasted a few seconds on each day	Somewhat Irritating (Test) Somewhat Gentle (Control)
SW (T only)	Moderate burning on the right cheek only	Day 1 that lasted for one hour	Somewhat Irritating (Test) Somewhat Gentle (Control)
MH (T>C)	Mild to severe stinging on both sides of the cheek	Days 1-5 that lasted one to three minutes on each day	Very Irritating (Test) Somewhat Irritating (Control)
JB (T=C)	Mild to moderate stinging on both sides of the cheek	Days 1-5 that lasted about one minute after application on each day	Very Irritating (Test) Somewhat Irritating (Control)

GC, SW, MH, and JB did not have any visible clinical changes. SW's subjective discomfort did not worsen despite continued use. [redacted] Serum [redacted] performed marginally with regards to subjective discomfort and will be further evaluated in a 4 week Dermatologist supervised Clinical Use study.

Gentleness Questionnaire

On the last visit the panelists rated the gentleness of each product. The majority of the panel rated both products either Very or Somewhat Gentle. GC, MH, JB, and SW all rated the products as somewhat irritating or very irritating due to their subjective comments (see Subjective Discomfort).

Prepared By: [redacted]
Senior Technician

Approved By: [redacted]
Program Manager

[redacted]

STUDY REF.# [redacted]

Serum contains 17.84% Propylene Carbonate

SUMMARY

[redacted] Serum [redacted] was tested via a four-week Dermatologist-supervised Clinical Use study. The study was a single-blind, baseline controlled monadic design with Dr. [redacted], a Board Certified Dermatologist, as the principal investigator. Panelists were instructed to apply the product once daily, in the morning, in place of any other anti-aging facial treatment products. Panelists were allowed to use their own facial moisturizer, if needed.

The Dermatologist did not observe any **visible clinical irritation** specifically related to use of [redacted] Serum.

Four panelists reported perceived discomfort/irritation while using [redacted] Serum. Two of the responses resolved spontaneously, without recurrence. One was episodic and limited to a specific set of conditions, i.e. application close to the eyelid margin. The remaining response was determined not to be specifically related to use of [redacted]. These responses will not reflect negatively upon the overall safety in use of [redacted] Serum.

Reported By: [redacted]
[redacted]
Associate Clinical Scientist

Approved By: [redacted]
[redacted] Ph.D.
Senior Manager

[redacted]
[redacted], M.D.
Consulting Dermatologist

STUDY REF. # [redacted]

TO: [redacted]

FROM: [redacted]

DATE: December 20, 2004

SUBJECT: Clinical Use Test Results of [redacted] Serum [redacted]

SUMMARY

[redacted] Serum # [redacted] was tested via a four-week Dermatologist-supervised Clinical Use study. The study was a single-blind, baseline controlled monadic design with Dr. [redacted] a Board Certified Dermatologist, as the principal investigator. Panelists were instructed to apply the product once daily, in the morning, in place of any other anti-aging facial treatment products. Panelists were allowed to use their own facial moisturizer, if needed.

The Dermatologist did not observe any **visible clinical irritation** specifically related to use of [redacted] Serum.

Four panelists reported perceived discomfort/irritation while using [redacted] Serum. Two of the responses resolved spontaneously, without recurrence. One was episodic and limited to a specific set of conditions, i.e. application close to the eyelid margin. The remaining response was determined not to be specifically related to use of [redacted] These responses will not reflect negatively upon the overall safety in use of [redacted] Serum.

STUDY OBJECTIVES

- To determine the potential of [redacted] Serum [redacted] to evoke clinical irritation and/or panelist-perceived discomfort/irritation when used under consumer use conditions.

TEST DESIGN

A total of fifty (50) individuals completed this four-week, Dermatologist-supervised Clinical Use Test. Actual test design and product identification are presented in Appendix I. Product use instructions are presented in Appendix II. Panelist demographics are listed in the study file.

STUDY DATES

September 14, 2004 - October 12, 2004

RESULTS: DERMATOLOGIST-ASSESSED VISIBLE IRRITATION

The Dermatologist did not observe any product related irritation. A tabulation of clinical changes may be found in Appendix III.

The Dermatologist observed a slightly greater level of positive versus negative changes in clinical skin conditions. Assessed changes were observed mainly in the categories of scaling and acne conditions, including papules and pustules, with the majority being in the acne category. The Dermatologist felt that all changes observed during the study period were within the parameters for normally occurring fluctuations in facial conditions in the general population.

One panelist reported fluctuating acne breakout throughout the study period. The Dermatologist did observe changes in acne activity at the interim and final visits; the panelist was initially assessed with acne related conditions. This panelist has a personal, and testing, history of acne conditions. The Dermatologist determined that her response was a normally occurring fluctuation in the panelist's pre-existing acne condition. As such, it will not reflect negatively upon the overall safety in use of [redacted] This panelist also experienced episodic burning that was slight in intensity. The burning resolved spontaneously, without recurrence, despite continued product use. (see PERCEIVED IRRITATION below)

PERCEIVED IRRITATION

Four panelists (8%) reported experiencing episodes of subjective discomfort during the study period. No follow-up testing was conducted.

Three panelists reported episodic discomfort, i.e. burning, on the skin. All three responses were slight in intensity and transient in duration, lasting from a few seconds to a few minutes. In each case, the response resolved spontaneously, without recurrence, despite continued product use.

One panelist reported episodic discomfort, i.e. burning, in the eyes. The discomfort was limited to a specific set of conditions, i.e. application close to the lid margins; the panelist did not experience any discomfort when applying the product a short distance from the lid margins. The discomfort was slight in intensity, lasted only a couple of seconds each time; it was not accompanied by any visible irritation. The panelist attributed the discomfort to the fumes from the product itself. Eye area discomfort is addressed via the product's pre-existing "Avoid contact with eyes." caution.

One panelist, who also experienced episodic burning on the skin, reported fluctuating acne activity which was determined to be a normally occurring fluctuation of a pre-existing acne condition. (see VISIBLE IRRITATION above)

Detailed Case Chronologies may be found in Appendix IV.

CONCLUSION

[redacted] Serum [redacted] exhibited acceptable results. There were no instances of product-induced clinical and/or panelist-perceived irritation.

Prepared By: [redacted]

Approved By: [redacted]

cc: [redacted]

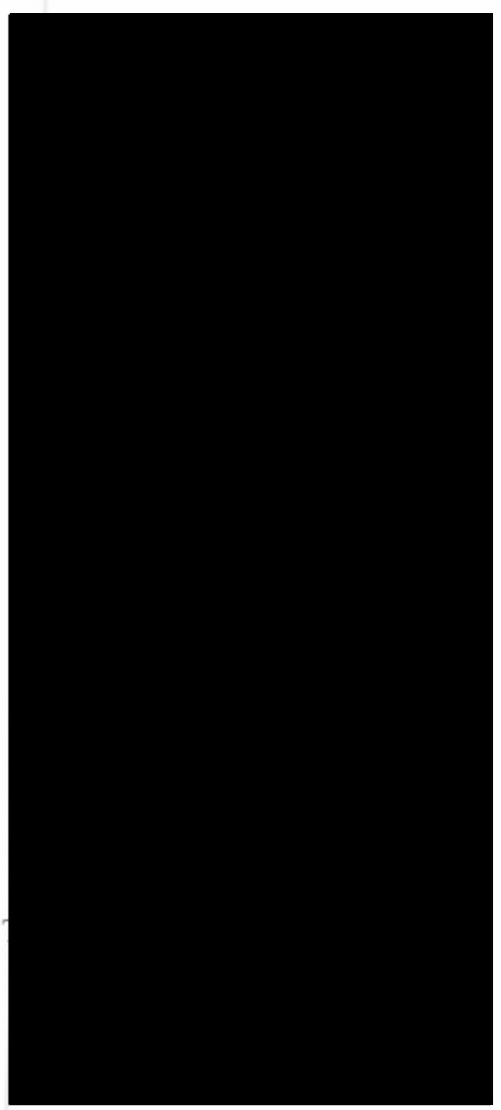
APPENDIX I

TEST DESIGN

Fifty (50) panelists completed a four-week, Dermatologist-supervised clinical use test. The panel was conducted as single-blind, baseline controlled monadic design evaluation.

The test product was supplied to all of the panelists for the 4-week evaluation period.

Test products were packaged in 1 oz. glass jars with dropper applicators and labeled with product type, i.e. FACIAL TREATMENT. Products were supplied to panelists with use instructions. Dermatologist-assessed facial exams were conducted initially, at the two-week interim visit and upon completion of the study. Questionnaires seeking panelist perceived problems were completed by the panelists at the end of each two-week study period.



APPENDIX II

USE INSTRUCTIONS
[redacted]
FACIAL TREATMENT

USE THIS PRODUCT ONCE A DAY, IN THE MORNING !!

WHILE PARTICIPATING IN THIS STUDY DO NOT USE PRODUCTS CONTAINING:
ALPHA-HYDROXY ACID (FOUND IN MANY ANTI-AGING PRODUCTS)
OR
SALICYCLIC ACID (FOUND IN MANY ACNE TREATMENT PRODUCTS)

TO USE:
1. Apply this product once daily, in the morning.
2. Cleanse face as usual.
3. Using dropper, dispense **3 to 4 drops** onto your palm.
4. Using fingertips, smooth over entire face, including the undereye and crowsfeet areas. AVOID CONTACT WITH EYES. Be sure to apply the product over dark spots, broken capillaries/spider veins and uneven skin tone areas.
5. You may continue to use your regular facial moisturizer and makeup products following application of the Facial Treatment.

NOTE: If prolonged sun exposure is unavoidable during the study period, we recommend use of a sunscreen of SPF 30 or greater on the face during exposure times.
For external use only.
Avoid contact with eyes. If product comes in contact with the eyes, rinse thoroughly with water.
Keep out of reach of children.

REMEMBER:
1. Bring your product with you on the exam dates (September 28th and October 12th).
2. This product is for your use only. Do not let other members of your family use it
3. Should any problems arise while using the product, please call the [redacted] and ask for [redacted].

APPENDIX III

Total Tabulation of Clinical Changes
Dermatologist- Supervised
N=51*

	Test	
	#	%
# of panelists that exhibited a change**	20	40
# of panelists that exhibited no change	30	60

	Test
Scaling	
increased	2
decreased	5
Acne	
increased	7
decreased	9
Inflamed Papules	
increased	3
decreased	6
Papules	
increased	0
decreased	1
Pustules	
increased	4
decreased	2
Rosacea	
increased	1
decreased	0

* - One panelist dropped from the study due to non-product related reasons.
** - Panelists may have exhibited more than one change.

APPENDIX IV

PANELIST-PERCEIVED DISCOMFORT/IRRITATION

[redacted]

AD #15	Self-Assessed Skin Sensitivity:	Normal
	Self-Assessed Skin Type:	Normal to Dry
	Facial Cleanser User:	Various
	Facial Moisturizer User:	Various
	Anti-Aging Treatment Products User:	Various

CASE CHRONOLOGY

9/14/04 AD reported to the [redacted] for her scheduled initial visit. She was given [redacted] Serum to use once daily, in the morning, for four weeks. Panelists were allowed to continue use of their own regular facial moisturizer, if desired.

She was Dermatologist-assessed as having slight central facial telangiectasia.

9/28/04 AD returned to the [redacted] for her scheduled interim visit. She stated that, on the first day of Serum use, she experienced a stinging sensation on the crowsfoot area only. The stinging was slight in intensity, lasting a couple of seconds each time; the discomfort was not accompanied by any visible signs of irritation, i.e. redness. Following the first day of use, the panelist did not experience any discomfort when using the Serum.

She was Dermatologist-assessed as having pre-existing slight central facial telangiectasia. (no change)

Instructions: The panelist will continue product use. She will contact the [redacted] if her response recurs. She will return to the [redacted] for her scheduled final visit.

10/12/04 AD returned to the [redacted] for her scheduled final visit. She stated that she did not experience any further episodes of discomfort while using the Serum.

The panelist was Dermatologist-assessed as having pre-existing slight central facial telangiectasia. (no change)

Judgment: No follow-up testing was conducted. The panelist's response was sporadic and transient, resolving spontaneously despite continued product use.

APPENDIX IV (cont.)

PANELIST-PERCEIVED DISCOMFORT/IRRITATION

[redacted]

DG #39	Self-Assessed Skin Sensitivity:	Normal
	Self-Assessed Skin Type:	Normal
	Facial Cleanser User:	Aveeda
	Facial Moisturizer User:	Oil of Olay
	Anti-Aging Treatment Products User:	None

CASE CHRONOLOGY

9/14/04 DG reported to the [redacted] for her scheduled initial visit. She was given [redacted] Serum to use once daily, in the morning, for four weeks. Panelists were allowed to continue use of their own regular facial moisturizer, if desired.

She was Dermatologist-assessed as having scaling of the upper lip with one inflamed papule of the upper lip and slight central facial telangiectasia.

9/28/04 DG returned to the [redacted] for her scheduled interim visit. She stated that, on the first couple of days of Serum use, she experienced a burning sensation around the nose only. The burning was slight in intensity, lasting a couple of seconds each time; the discomfort was not accompanied by any visible signs of irritation, i.e. redness. Following the first couple days of use, the panelist did not experience any discomfort when using the Serum. DG noted that she has experienced a similar response when using other alcohol-containing products on the face.

She was Dermatologist-assessed as having one inflamed papule of the chin and one inflamed papule of the left cheek with pre-existing slight central facial telangiectasia. Scaling of the upper lip was clear.

Instructions: The panelist will continue product use. She will contact the [redacted] if her response recurs. She will return to the [redacted] for her scheduled final visit.

10/12/04 DG returned to the [redacted] for her scheduled final visit. She stated that she has not experienced any further episodes of discomfort while using the Serum.

The panelist was Dermatologist-assessed as having pre-existing slight central facial telangiectasia. Inflamed papules were clear.

Judgment: No follow-up testing was conducted. The panelist's response was sporadic and transient, resolving spontaneously despite continued product use.

APPENDIX IV (cont.)

PANELIST-PERCEIVED DISCOMFORT/IRRITATION

[redacted]

AT #30	Self-Assessed Skin Sensitivity:	Normal
	Self-Assessed Skin Type:	Normal to Dry
	Facial Cleanser User:	NuSoap
	Facial Moisturizer User:	Kinerase
	Anti-Aging Treatment Products User:	Kinerase

CASE CHRONOLOGY

9/14/04 AT reported to the [redacted] for her scheduled initial visit. She was given [redacted] Serum to use once daily, in the morning, for four weeks. Panelists were allowed to continue use of their own regular facial moisturizer, if desired.

She was Dermatologist-assessed as having generalized telangiectasia.

9/28/04 AT returned to the [redacted] for her scheduled interim visit. She stated that, while using the Serum, she experienced episodes of burning in the eyes. The discomfort occurred only on occasions when the panelist applied the product too close to her eyes. The burning was slight in intensity, lasting a couple of seconds each time; the discomfort was not accompanied by any visible signs of irritation, i.e. redness. The panelist did not experience any discomfort in the eyes if she kept application at the cheekbone or below nor did she experience any discomfort on the skin where the product was applied. AT attributed the discomfort directly to the product fumes.

She was Dermatologist-assessed as having an excoriated papule of the glabella with pre-existing generalized telangiectasia.

Instructions: The panelist will continue product use. She will continue to take care not to apply the product too close to her eyes. AT will contact the [redacted] if her response recurs. She will return to the [redacted] for her scheduled final visit.

10/12/04 AT returned to the [redacted] for her scheduled final visit. She stated that, during the final two weeks of the study period, she continued to experience slight, transitory discomfort in the eye if she applied the product too close to the immediate eye area. AT noted again that she attributed the discomfort to the fumes from the product. The panelist was Dermatologist-assessed as having very slight scaling of the left nasolabial fold with pre-existing generalized telangiectasia. Excoriated papule was clear.

Judgment: No follow-up testing was conducted. The panelist's response was episodic and transient, and limited to a specific set of conditions, i.e. application close to the lid margin area.

APPENDIX IV (cont.)

PANELIST-PERCEIVED DISCOMFORT/IRRITATION

[redacted]

AU #9	Self-Assessed Skin Sensitivity:	Normal
	Self-Assessed Skin Type:	Normal to Oily
	Facial Cleanser User:	Dove
	Facial Moisturizer User:	Jergens
	Anti-Aging Treatment Products User:	None

CASE CHRONOLOGY

9/14/04 AU reported to the [redacted] for her scheduled initial visit. She was given [redacted] Serum to use once daily, in the morning, for four weeks. Panelists were allowed to continue use of their own regular facial moisturizer, if desired.

She was Dermatologist-assessed as having multiple open and closed comedones of the chin and forehead, inflamed papules of the chin (6) and right cheek (1), hyperpigmentation of the eyelid and central facial telangiectasia.

9/28/04 AU returned to the Testing Center for her scheduled interim visit. She stated that, with each use of the Serum, she experiences a burning sensation. The burning is slight in intensity (though the intensity is mild when product is applied over acne blemishes) and lasts a few minutes each time. The discomfort is not accompanied by any visible signs of irritation, i.e. redness. AU noted that she has experienced a similar response when using other alcohol-containing products on the face. The panelist also noted increased acne breakout while using the Serum. She noted that, after about one and one-half weeks of Serum use, she began to observe any increase in acne activity on her face. As the increased breakout is relatively recent, AU was uncertain if the blemishes were fluctuating in nature or steadily worsening with continued use.

She was Dermatologist-assessed as having inflamed papules of the chin (3), cheeks (3) and forehead (1) with pre-existing multiple open and closed comedones of the chin and forehead, hyperpigmentation of the eyelids and central facial telangiectasia.

Instructions: The panelist will continue product use. She will be contacted in several days to check on the progress of her acne activity. She will return to the [redacted] for her scheduled final visit.

10/1/04 AU was contacted by [redacted] She stated that her acne breakout seemed to be slightly improved. She has continued to use the Serum.

APPENDIX IV (cont.)

PANELIST-PERCEIVED DISCOMFORT/IRRITATION

[redacted]

Instructions: The panelist was instructed to continue product use. She will contact the [redacted] if her response worsens in intensity. She will return to the [redacted] for her scheduled final visit.

10/12/04 AU returned to the [redacted] for her scheduled final visit. She stated that, during the final two weeks of the study period, she continued to experience fluctuating acne breakout. However, AU did not experience any further episodes of burning while using the Serum.

The panelist was Dermatologist-assessed as having four inflamed papules of the cheeks and six inflamed papules of the forehead with pre-existing multiple open and closed comedones of the chin and forehead, hyperpigmentation of the eyelids and central facial telangiectasia.

Judgment: No follow-up testing was conducted. The panelist's response of burning was sporadic and transient, resolving spontaneously despite continued product use. Her response of acne breakout, though corroborated by the Dermatologist during the study period, was determined to be a fluctuation of her pre-existing acne condition and not specifically related to use of the Serum. The panelist's assessment with acne related conditions at the initial visit of this study, her personal acknowledgement of a history of pre-existing acne conditions, a testing history of assessed acne conditions in conjunction with a discussion with the consulting Dermatologist for this study, [redacted], led to this determination. This response will not reflect negatively upon the overall safety in use of the Serum.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: May 30, 2023

SUBJECT: Propylene Carbonate

Anonymous. 2004. An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay (product contains 17.84% Propylene Carbonate).

[redacted]

FINAL REPORT September 7, 2004

[redacted]

Sample: [redacted]

[redacted]

[redacted]

Title: An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

product contains 17.84% Propylene Carbonate

Sponsor: [redacted]

Principal Investigator: [redacted] (Board Certified Dermatologist)

Testing Facility: [redacted]

Protocol: [redacted]

Final Report Date: **September 7, 2004**

[redacted]

September 7, 2004
Date

Principal Investigator

"The names of [redacted] any officer, employee, or collaborating scientist are not to be used for any advertising, promotional or sale purposes without the written consent of [redacted]

F I N A L R E P O R T

[redacted]

SPONSOR:

[redacted]

SPONSOR STUDY:

Authorization Letter Dated: July 20, 2004

STUDY TITLE:

Evaluation of the contact-sensitizing potential of a coded topically-applied test agent.

STUDY OBJECTIVE:

The objective of this study is to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

TEST MATERIAL:

The test sample, supplied by the sponsor, was a product labeled [redacted] and tested as supplied.

[redacted]

TEST PRODUCT ACCOUNTABILITY:

All test samples and materials were received in good condition by our Quality Assurance Department. The test materials and quantities were checked for (1) amount (2) product number or code (3) material container etc. The materials were individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). All test materials were stored under ambient conditions in an inaccessible location under the supervision of the investigator.

PRINCIPAL INVESTIGATOR:

[redacted] (Board Certified Dermatologist)

[redacted]

[redacted]

[redacted]

[redacted] ADMINISTRATIVE STRUCTURE:

[redacted] (Screening, Patch Applications/Removals, Recognize AE's)

[redacted] (Expert Grader)

[redacted] (Panel Recruitment and Initial Screening)

TESTING FACILITY:

[redacted]

[redacted]

[redacted]

[redacted]

CONDUCTION DATES:

This study was conducted from July 26, 2004 through August 27, 2004

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics. The criteria for exclusion were:

1 - History of sun hypersensitivity and photosensitive dermatoses

2 - History of drug hypersensitivity or recurrent dermatological diseases

3 - Pregnancy or mothers who are breastfeeding

4 - Scars, moles or other blemishes over the test site which can interfere with the study

5 - Recent sunburn

6 - Subjects receiving systemic or topical drugs or medications, including potential sensitizers within the previous 4 weeks

7 - Other medical conditions considered by the investigator as sound reasons for disqualification from enrollment into the study.

INFORMED CONSENT:

After the protocol, reasons for the study, possible associated risks and potential benefits or risks of the treatment had been completely explained, signed, informed subject consent was obtained from each volunteer prior to the start of the study. Copies of all consent forms are on file at [redacted]

[redacted]

METHOD:

Patches were applied to the upper outer arm, volar forearm or the back of each subject. The entire test was composed of two distinct phases: (1) an Induction phase and (2) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material was applied to the same site before the site was again covered with occlusive tape (induction patch). Since the test material coded [redacted] contained volatile ingredients, it was allowed to air-dry for ~30 minutes prior to application to the test site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

[redacted]

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Challenge Phase**:

After a ten day rest period which follows the last induction patch application, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm or side of back in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded 15-30 minutes later and again 24 hours later for any reaction.

[redacted]

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	**GRADES:**	**CLASSIFICATION**:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

RESULTS:

A total of twenty-six (26) healthy, adult volunteers of both sexes who satisfied the inclusion criteria were enrolled into this study. There were 24 females and 2 males. Their ages ranged from 27 to 65 years. All 26 subjects completed this investigation as outlined in the standard protocol.

[redacted] [redacted].

The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled [redacted] and coded [redacted] does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

[redacted]

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

[redacted]

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	[redacted]	39	F	C
02	[redacted]	36	F	C
03	[redacted]	48	F	C
04	[redacted]	53	F	C
05	[redacted]	45	F	C
06	[redacted]	38	F	C
07	[redacted]	47	F	C
08	[redacted]	51	F	C
09	[redacted]	44	F	C
10	[redacted]	62	F	C
11	[redacted]	41	F	C
12	[redacted]	43	F	C
13	[redacted]	34	F	C
14	[redacted]	45	M	C
15	[redacted]	35	F	C
16	[redacted]	44	F	C
17	[redacted]	44	F	C
18	[redacted]	65	F	C
19	[redacted]	53	F	C
20	[redacted]	38	F	C
21	[redacted]	32	F	C
22	[redacted]	27	F	C
23	[redacted]	53	F	C
24	[redacted]	35	F	C
25	[redacted]	46	M	C
26	[redacted]	53	F	C

C = Caucasian

[redacted] _____ [redacted].

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: [redacted]

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0
26	0	0

Challenge Readings:

48-Hour Reading – August 26, 2004
72-Hour Reading – August 27, 2004