Safety Assessment of Propylene Carbonate as Used in Cosmetics

Status:	Re-Review for Panel Consideration
Release Date:	February 10, 2023
Panel Meeting Date:	March 6 – 7, 2023

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. This safety assessment was prepared by Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR.

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1620 L Street, NW, Suite 1200 ◇ Washington, DC 20036-4702 ◇ ph 202.331.0651
cirinfo@cir-safety.org

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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: February 10, 2023
Subject: Re-Review of the Safety Assessment of Propylene Carbonate

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a review of the safety of Propylene Carbonate in 1987 (identified as *originalreport_PropyleneCarbonate_032023* in the pdf), with the conclusion that this ingredient is safe as a cosmetic ingredient in the present practices of use and concentration, as stated in that report. The Panel previously considered a re-review of this report and reaffirmed the 1987 conclusion, as published in 2006 (*rereview2006_PropyleneCarbonate_032023).*

Because it has been 15 years since the previous re-review was published, in accord with Cosmetic Ingredient Review (CIR) Procedures, the Panel should consider whether the safety assessment of Propylene Carbonate should be re-opened. An extensive search of the world's literature was performed for studies dated 1999 forward. An historical overview, comparison of original and new use data, the search strategy used, and a synopsis of notable new data are enclosed herein (*newdata_PropyleneCarbonate_032023*).

New toxicological studies were found for several toxicological endpoints (metabolism, dermal penetration, dermal and oral toxicity, reproductive toxicity, genotoxicity, carcinogenicity, dermal irritation, and ocular irritation). In addition, a case report was found on a patient experiencing pruritic erythematous scaly plaques with a positive patch test to a mixture containing Propylene Carbonate. It should be noted that Propylene Carbonate is used at up to 5% as an inactive ingredient in an FDA-approved topical drug formulation.

Also included for your review is a table of current and historical use data (*usetable_PropyleneCarbonate_032023*). (As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use is presented both cumulatively by likely duration and exposure and individually by product category.) Since this ingredient was last considered for re-review, the frequency of use for Propylene Carbonate has significantly increased from 178 uses reported in 2002 to 911 uses reported in 2022. In addition, the concentration of use for this ingredient has also increased significantly. In 2003, Propylene Carbonate was reported to be used at up to 5%. According to 2022 concentration of use data, Propylene Carbonate is used at up to 17.9% (in night products (not spray)). It should be noted that Propylene Carbonate is now reported to be used in baby products (concentration of use not reported for these uses).

If upon review of the new information and updated use data the Panel determines that a re-review is warranted, a Draft Amended Report will be presented at an upcoming meeting.

Re-Review - Propylene Carbonate - History and New Data

(Priya Cherian – March 2023)

Ingredient (1)	Citation	Conclusion	Use - New Data	Results	Use - Existing Data	Results	Notes
Propylene Carbonate	JACT 6(1):23-51, 1987 IJT 25(Suppl. 2) :1-89,2006	safe as used reaffirmed	frequency of use (2022) conc of use (2022)	911 ≤ 17.9%	frequency of use (2002) conc of use (2003)	178 ≤ 5%	Significant increase in frequency of use and concentration; uses now reported in baby products

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
https://ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.simple	European Union–CosIng	Propylene Carbonate is not restricted for use in cosmetics according to the EU CosIng database	Not included in original report
40CFR180.950 *https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-180/subpart-D/section-180.950*	Non-Cosmetic Use	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 FFDCA section 408, if such use is in accordance with good agricultural or manufacturing practices	Not included in original report
https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm	Non-Cosmetic Use	Propylene Carbonate is used as an inactive ingredient at up to 5% in an FDA-approved topical ointment (drug product)	Not included in original report
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/2/2	ADME – Metabolism	In vitro assay using blood from Wistar rats; blood incubated with 1 mM Propylene Carbonate; incubation at intervals up to 30 min.; the calculated half-life value of propylene carbonate was 0.734 min; hydrolysis product of propylene glycol	No ADME data included in original report
Ursin C, Hansen CM, Van Dyk JW, Jensen PO, Christensen IJ, Ebbehoej J. Permeability of commercial solvents through living human skin. Am Ind Hyg Assoc J. 1995 Jul;56(7):651-60. doi: 10.1080/15428119591016665. PMID: 7618604.	Dermal Penetration	in vitro assay using female human breast skin; Franz diffusion cell; exposed skin area: 0.64 cm^2; stretched skin thickness of 300-600 µm; [^{3}H] water permeation rate used as criteria for defective skin samples; samples taken from collection chamber at times of 0.16, 0.33, 0.5, 1, 2, 4, and 6 h; the normalized permeability constant of Propylene Carbonate in an intact specimen was 0.2 (**two of the three specimens were considered defective**)	No dermal penetration data was included in the original report
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Acute Toxicity – Dermal	OECD TG 402; 3000 mg/kg bw of undiluted Propylene Carbonate; New Zealand White rabbits (5/sex); 24 h exposure under occlusive conditions; 14-d observation period; $LD_{50} \geq 3000$ mg/kg bw	No
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Short-Term Toxicity – Oral	OECD TG 407; Sprague-Dawley rats (5/sex/group); 28-d treatment period; 500, 1000, 2000, 3000, and 5000 mg/kg bw/d undiluted Propylene Glycol given in deionized water via gavage; no mortality; statistically-significant, dose-dependent increase in absolute female ovary weights in animals dosed with 3000 and 5000 mg/kg bw/d; statistically significant decrease in female liver weights in 1000 and 5000 mg/kg bw/d dose groups; significantly larger testes weights in males of the 5000 mg/kg bw/d group	No short-term oral toxicity data included in original report

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Short-Term Toxicity - Inhalation	OECD TG 412; Fischer 344/CDF rats (5/sex/group); 9-d exposure; whole-body exposure to 1000, 2500, and 5000 mg/m^3 Propylene Carbonate; no mortality; highest tested concentration produced minor toxicological changes to the eyes, mucous membranes, and nasal cavities	Inhalation toxicity studies in original report did not report ocular irritation/toxicity
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Subchronic Toxicity – Oral	OECD TG 408; Sprague-Dawley rats (15/sex/group); 90-d treatment period; 1000, 3000, and 5000 mg/kg bw/d undiluted Propylene Glycol given in deionized water via gavage; NOAEL > 5000 mg/kg bw/d	No subchronic oral toxicity data included in original report
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Subchronic Toxicity - Inhalation	OECD TG 413; Fischer 344 rats (15/sex/group); 93-d treatment period; whole-body exposure to 100, 500, and 1000 mg/m^3 aerosolized Propylene Carbonate; 6 h exposures/d; NOAEC = 1000 mg/m^3; swollen periocular tissue observed in 2 animals of the 500 mg/m^3 group and 4 animals of the 1000 mg/m^3 group	Inhalation toxicity studies in original report did not report ocular irritation/toxicity
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	DART	Sprague-Dawley rats (6 females/group); treated with undiluted Propylene Carbonate (up to 2000 mg/kg bw/d) on gestation days 6-15 via gavage; no statistically-significant adverse effects in fetuses or dams	No DART studies provided in original report
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	DART	OECD TG 414; Sprague-Dawley rats (27 females/group); treated with undiluted Propylene Carbonate (1000, 3000, and 5000 mg/kg bw/d) on gestation days 6-15 via gavage; no developmental toxicity observed; maternal toxicity reported as dam mortality, reduced body weight gain, and reduction in food consumed observed at 3000 mg/kg/d; developmental toxicity NOAEL > 5000 mg/kg bw/d; maternal toxicity = 1000 mg/kg bw/d	No DART studies provided in original report
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Genotoxicity – In Vitro	Ames assay; *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100; treatment with 10-1000 µg/plate Propylene Carbonate, with and without metabolic activation; non-genotoxic	No
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Genotoxicity – In Vivo	OECD TG 474; mammalian erythrocyte micronucleus test; CD-1 mice (5/sex); intraperitoneal injection of 1666 mg/kg bw Propylene Carbonate in water; non-genotoxic	No
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Carcinogenicity – Dermal	OECD TG 451; C3H/HeJ male mice (n = 50); animals treated dermally with 50 µl undiluted Propylene Carbonate 2x/wk for 104 wk (level of occlusion not stated); non-carcinogenic	Carcinogenicity data not provided in original report
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Dermal Irritation - Animal	0.5 g undiluted Propylene Carbonate applied to skin of Vienna White rabbits (n = 4) under occlusive conditions for 20 h; mean erythema and edema scores of 0; non-irritating	Animal dermal irritation assays in original predominantly reported slight irritation
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Ocular Irritation – In Vitro	HET-CAM assay; treatment with 10, 20, 40, 60, 80 or 100% Propylene Carbonate in a tradename wetting agent or double-distilled water (0.3 ml); category 1 irritant (irreversible effect on the eye); EC_{90} = 17%	No in vitro ocular irritation data was provided in original report; original report reported mainly slight to moderate irritation in rabbit eyes
Donahue DA, Avalos J, Kaufman LE, Simion FA, Cerven DR. Ocular irritation reversibility assessment for personal care products using a porcine corneal culture assay. Toxicol In Vitro. 2011 Apr;25(3):708-14. doi: 10.1016/j.tiv.2010.12.008. Epub 2010 Dec 21.	Ocular Irritation – In Vitro	Porcine corneal opacity reversibility assay; test article: hair glazing product containing 15-25% Propylene Carbonate, 1-5% citric acid, and 5-10% ethanol; decreased cellularity of the superficial squamous cell layer observed in corneas (reversible damage); no effects on any other layer of the cornea	No in vitro ocular irritation data was provided in original report; original report reported mainly slight to moderate irritation in rabbit eyes

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Ocular Irritation – Animal	OECD TG 405; Undiluted Propylene Carbonate (0.1 ml) applied to eyes of New Zealand White rabbits (n = 3); observed for 10 d; moderate irritant (class 5 of a 1-8 scale)	No
https://echa.europa.eu/da/registration-dossier/-/registered-dossier/16088/7/3/2/?documentUUID=3df3d523-5468-4b42-b5c0-8f6729bbaa75	Ocular Irritation – Animal	OECD TG 405; Undiluted Propylene Carbonate (0.1 ml) applied to eyes of New Zealand White rabbits (n = 3); observed for 7 d; moderate irritant (class 5 of a 1-8 scale)	No
Luna-Bastante L, Gatica-Ortega ME, Pastor-Nieto MA, Vergara-de-la-Campa L, Gómez-Dorado BA, Alonso-Naranjo L, Pérez-Hortet C. Allergic contact dermatitis to Tinosorb S, Scutellaria baicalensis, and other emerging allergens in cosmetics. Contact Dermatitis. 2020 May;82(5):307-309. doi: 10.1111/cod.13460. Epub 2020 Jan 11. PMID: 31879957.	Case Report	A 39-yr-old female consulted with a 2-yr history of pruritic erythematous scaly plaques in the eye region that responded to topical corticosteroids and pimecrolimus; patch tests were performed using the patient's own products, including a foundation containing Propylene Carbonate. The foundation itself and a mixture of Propylene Carbonate, cyclopentasiloxane, and disteardimonium hectorite yielded positive patch test results (Propylene Carbonate was not patch tested alone). Patch test results were also positive for a BB cream, Bis-ethylhexyloxyphenol methoxyphenyl triazine, *Scutellaria baicalensis* root extract, propylene glycol, and a mixture of talc, Cl 77 491, and dimethicone/methicone copolymer.	No case reports were included in the original report.

ADME = absorption, distribution, metabolism, and excretion; DART = developmental and reproductive toxicity; EC_{90} = estimated concentration what causes effects indicative of serious eye damage within 90 seconds; HET-CAM = hen's egg chorioallantoic membrane; LD_{50} = median lethal dose; NOAEC = no-observed-adverse-effect-concentration; NOAEL= no-observed-adverse-effect-level; OECD TG = Organisation for Economic Co-operation and Development Test Guidelines; TCA = trichloroacetic acid

Search (from 1999 on)
PubMed
((("propylene carbonate") OR (108-32-7 [CAS No.])) AND (("1999"[Date - Publication] : "3000"[Date - Publication])) – 843 hits; 2 useful

FDA
("propylene carbonate")

EU COSING
("propylene carbonate")

ECHA
("propylene carbonate")

Table 1. 2022 and historical frequency and concentration of use according to likely duration and exposure and by product category

	# of Uses		*Max Conc of Use (%)*	
	2022[1]	**2002[2]**	**2022[3]**	**2003[2]**
	Propylene Carbonate			
Totals	**911**	**178**	**0.0064 -17.9**	**0.003 - 5**
summarized by likely duration and exposure*				
Duration of Use				
Leave-On	*894*	*139*	*0.0064 – 17.9*	*0.003 – 5*
Rinse-Off	*17*	*38*	*0.24 – 6*	*0.1 – 2*
Diluted for (Bath) Use	*NR*	*1*	*NR*	*NR*
Exposure Type*				
Eye Area	231	68	0.01 – 2.7	0.2 - 4
Incidental Ingestion	381	35	0.0064 – 3.9	0.03 – 2
Incidental Inhalation-Spray	28[a]; 22[b]	7[a]	0.28	0.02 – 0.2[a]
Incidental Inhalation-Powder	7; 22[b]; 2[c]	NR	1.4; 0.05 – 6[c]	0.4
Dermal Contact	467	113	0.01 – 17.9	0.02 – 5
Deodorant (underarm)	1[a]	2[a]	0.93 – 1.4	0.2 – 5[a]
Hair - Non-Coloring	3	1	0.24	NR
Hair-Coloring	4	1	NR	NR
Nail	11	6	0.15 – 6	0.003 – 4
Mucous Membrane	382	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	17	6	0.08 – 0.36	0.3
Eyeliner	69	15	0.14 – 2.7	0.2 – 0.6
Eye Shadow	50	10	0.01 – 0.7	0.4 – 1
Eye Lotion	3	NR	NR	NR
Eye Makeup Remover	5	3	NR	NR
Mascara	45	22	0.75 – 2.2	2 – 4
Other Eye Makeup Preparations	42	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	2	NR	NR	NR
Hair Coloring Preparations				
Hair Tints	4	NR	NR	NR
Other Hair Coloring Preparation	NR	1	NR	NR
Makeup Preparations				
Blushers (all types)	14	1	0.04 – 0.76	1 – 2
Face Powders	7	NR	1.4	0.4
Foundations	75	3	0.16 – 0.45	0.6 – 2
Leg and Body Paints	2	NR	NR	NR
Lipstick	381	35	0.0064 – 3.9	0.03 - 2
Makeup Bases	28	4	0.03 – 0.075	NR
Rouges	1	NR	NR	0.1
Makeup Fixatives	1	2	NR	NR
Other Makeup Preparations	79	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	4	NR	1.1	0.003
Nail Polish and Enamel Removers	3	6	6	1
Other Manicuring Preparations	2	NR	NR	4
Personal Cleanliness Products				
Deodorants (underarm)	1	2	0.93 – 1.4 (spray)	0.2 – 5
Other Personal Cleanliness Products	1	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)	11	NR	0.05 (not spray)	NR
Foot Powders and Sprays	NR	NR	0.28	NR
Moisturizing	20	4	0.45 (not spray)	0.02 – 0.2
Night	5	1	17.9 (not spray)	NR
Paste Masks (mud packs)	NR	1	NR	0.3 - 2
Skin Fresheners	1	NR	NR	NR

Table 1. 2022 and historical frequency and concentration of use according to likely duration and exposure and by product category

	# of Uses		*Max Conc of Use (%)*	
	2022[1]	**2002[2]**	**2022[3]**	**2003[2]**
Other Skin Care Preparations	16	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.

REFERENCES

1. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2022. Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2022; received January 11, 2022). College Park, MD.

2. Andersen FA (ed). Annual review of cosmetic ingredient safety assessments - 2004/2005. *IJT.* 2006;25:1-89.

3. Personal Care Products Council. 2022. Concentration of use by FDA product category: Propylene Carbonate. (Unpublished data submitted by Personal Care Products Council on November 22, 2022.)

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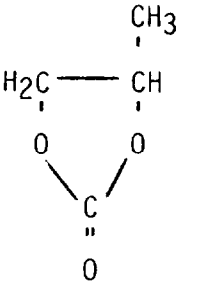
2

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-

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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]

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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]

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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

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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

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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-

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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.

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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

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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]

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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

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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

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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]

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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.

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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-

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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

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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

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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

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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

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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

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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

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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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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.

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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,

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

[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.