Amended Safety Assessment of Propylene Carbonate as Used in Cosmetics

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*All interested persons are provided 60 days from the above release date (i.e.**, by May 20, 2025**) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.*

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ABBREVIATIONS

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
FOU	frequency of use
GHS	globally harmonized system
HET-CAM	hen's egg chorioallantoic membrane
LD_{50}	median lethal dose
LLNA	local lymph node assay
l.o.	leave-on
LOAEC	lowest-observed-adverse-effect-concentration
LOAEL	lowest-observed-adverse-effect-level
MoCRA	Modernization of Cosmetics Regulation Act
MW	molecular weight
NOAEC	no-observed-adverse-effect-concentration
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
RLD	Registration and Listing Data
r.o.	rinse-off
SIOPT	single-insult occlusive patch test
TCA	trichloroacetic acid
TG	test guideline
US	United States
UV	ultraviolet
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

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

INTRODUCTION

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

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted in January 2025 for studies published in 2003 onwards. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

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

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

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[6] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited. In addition, it should be noted that data on a read-across ingredient, propylene glycol, were included in the ECHA dossier. However, since data for the relevant endpoints were found on Propylene Carbonate and are included herein, data on propylene glycol that were summarized in the ECHA dossier are not included in this CIR safety assessment.

CHEMISTRY

Definition and Structure

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

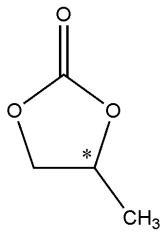

Figure 1. Propylene Carbonate

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

Chemical Properties

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

Method of Manufacture

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

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

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

Impurities

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

Ultraviolet (UV) Absorption

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

USE

Cosmetic

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

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

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

Propylene Carbonate is used in cosmetic sprays and powders, and could possibly be inhaled (e.g., foot powders and sprays at up to 0.28%, deodorant sprays and face powders, both at up to 1.4%). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable

(i.e., they would not enter the lungs) to any appreciable amount. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable. However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

Some products containing Propylene Carbonate may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined by the FDA, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available in some instances. Some of the reported product categories for this ingredient as listed in RLD do require designation if airbrush application is used, and this type of application was reported (e.g., foundations). Additionally, the Council currently surveys the cosmetic industry for maximum reported use concentrations of ingredients in products which may be used in conjunction with an airbrush delivery system; thus, this type of data may also be available when submitted. Please note that no concentration of use data were provided indicating airbrush application. Nevertheless, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

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

Non-Cosmetic

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

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

TOXICOKINETIC STUDIES

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

Dermal Penetration

In Vitro

The dermal penetration potential of Propylene Carbonate was evaluated in human breast skin samples (thickness of 1-2 mm; 3 total samples).[19] Water [^{3}H] was run through the diffusion cell system for 2 h prior to the test substance to calibrate the relative permeability of samples, and to detect defective specimens. Then, the challenge test was applied to skin samples, and 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

In Vitro

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

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

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

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

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

Oral

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

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

Inhalation

Propylene Carbonate was not lethal to 6 rats exposed to concentrated vapors for 8 h.[2] 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).

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

Repeated-Dose Toxicity Studies

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

Details on the repeated dose toxicity studies summarized below can be found in Table 3. Statistically significant adverse effects were observed in rats (5/sex/group) treated with Propylene Carbonate (up to 5000 mg/kg bw/d, in deionized water, via gavage) for 28 d (i.e., increased liver, ovary, and testes weights compared to controls (majority of adverse effects observed with 3000 or 5000 mg/kg bw/d)).[6] A no-observed-adverse-effect-level (NOAEL) of > 5000 mg/kg bw/d was established in an assay in which rats (15/sex/group) were given Propylene Carbonate (in deionized water, via gavage) at

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

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

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

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

GENOTOXICITY STUDIES

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

In Vitro

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

In Vivo

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

CARCINOGENICITY STUDIES

Dermal

The potential carcinogenicity of Propylene Carbonate (50 µl; tested neat) was evaluated in male Jackson C3H/HeJ mice (50/group).[6] A negative control group was left untreated and a positive control group was treated with 0.05% benzo(a)pyrene in acetone. Animals were administered the test substance via the dorsal skin, 2x/wk, for 104 wk (level of occlusion not stated). No treatment-related skin tumors were observed in the Propylene Carbonate-treated group. A squamous cell carcinoma was observed in the preputial gland duct of a treated mouse; however, this was not considered to be treatment-

related based on the site of origin, distance from the treatment site, and lack of evidence of preneoplastic or neoplastic change in the treatment area.

DERMAL IRRITATION AND SENSITIZATION STUDIES

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

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

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

Phototoxicity/Photosensitization

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

OCULAR IRRITATION STUDIES

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

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

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

SUMMARY

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

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

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

LD_{50}s of ≥ 2000 mg/kg bw and ≥ 3000 mg/kg bw were determined in 2 acute dermal toxicity assays performed in rabbits exposed to undiluted Propylene Carbonate under occlusive conditions. An LD_{50} of 27 ml/kg bw was determined in an acute oral toxicity assay performed using rats given 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. The local NOAEC was determined to be 100 mg/m^3 air.

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

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

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

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

A mean stain-retention score of 1.8 ± 1.5 on day 1 of treatment was observed in a porcine corneal opacity reversibility assay in which excised porcine eyes were exposed to a hair glazing product containing 15 – 25% Propylene Carbonate (mean retention score of negative control was 0.9 ± 1). An EC_{90} of 17% was determined in a HET-CAM assay in which eggs were incubated with 10 – 100% Propylene Carbonate in distilled water. Slight edema and cloudiness were observed 1 h after administration of Propylene Carbonate (tested neat; no vehicle) into the eyes of 3 rabbits (sex not stated). In another study using 3 rabbits, Propylene Carbonate (tested neat) was determined to be moderately irritating in an ocular irritation assay using rabbits. Conversely, undiluted Propylene Carbonate was considered to be non-irritating in a different ocular irritation assay performed in 6 rabbits.

DISCUSSION

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

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

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

The Panel reviewed the available inhalation toxicity data and discussed the issue of incidental inhalation exposure resulting from this ingredient; for example, Propylene Carbonate is reported to be used in face powders and deodorant sprays at up to 1.4% and could be possibly inhaled. The Panel noted that the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient. Coupled with the small actual exposure in the breathing zone, high systemic (1000 mg/m^3) and local (100 mg/m^3) NOAECs in a 13-wk inhalation performed in rats, and the low concentrations at which this ingredient is used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

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

CONCLUSION

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

TABLES

Table 1. Chemical properties

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

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

	# of Uses			Max Conc of Use	
	RLD (2024)[14]	VCRP (2023)[15]	VCRP (2002)[3]	% (2022)[16]	% (2003)[3]
Totals*	**13, 340**	**882**	**178**	**0.0064 -17.9**	**0.003 - 5**
summarized by likely duration and exposure**					
Duration of Use					
Leave-On	***	*874*	*139*	*0.0064 – 17.9*	*0.003 – 5*
Rinse-Off	***	*8*	*38*	*0.24 – 6*	*0.1 – 2*
Diluted for (Bath) Use	***	*NR*	*1*	*NR*	*NR*
Exposure Type					
Eye Area	***	204	68	0.01 – 2.7	0.2 - 4
Incidental Ingestion	***	389	35	0.0064 – 3.9	0.03 – 2
Incidental Inhalation-Spray	***	29[a]; 13[b]	7[a]	0.28	0.02 – 0.2[a]
Incidental Inhalation-Powder	***	7; 13[b]; 13[c]	NR	1.4; 0.05 – 6[c]	0.4
Dermal Contact	***	442	113	0.01 – 17.9	0.02 – 5
Deodorant (underarm)	***	33[a]	2[a]	0.93 – 1.4	0.2 – 5[a]
Hair - Non-Coloring	***	3	1	0.24	NR
Hair-Coloring	***	2	1	NR	NR
Nail	***	5	6	0.15 – 6	0.003 – 4
Mucous Membrane	***	389	62	0.0064 – 3.9	0.03 – 2
Baby Products	***	3	NR	NR	NR
as reported by product category					
Baby Products	***4***				
Baby Shampoos	3	NR	NR	NR	NR
Baby Lotions/Oils/Powders/Creams		2	NR	NR	NR
Other Baby Products	1 (l.o.)	1	NR	NR	NR
Bath Preparations	***1***				
Bath Oils, Tablets, and Salts	NR	NR	1	NR	NR
Bubble Baths	1	NR	NR	NR	NR
Eye Makeup Preparations (other than children's eye makeup preparations)	***2579***				
Eyebrow Pencil	258	15	6	0.08 – 0.36	0.3
Eyeliner	707	58	15	0.14 – 2.7	0.2 – 0.6
Eye Shadow	922	47	10	0.01 – 0.7	0.4 – 1
Eye Lotion	20	3	NR	NR	NR
Eye Makeup Remover	15	4	3	NR	NR
False Eyelashes	1	NA	NR	NR	NR
Mascara	360	44	22	0.75 – 2.2	2 – 4
Eyelash and Eyebrow Adhesives, Glues, and Sealants	35	NA	NR	NR	NR
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	104	NA	NR	NR	NR
Eyelash Cleansers	19	NA	NR	NR	NR
Other Eye Makeup Preparations	306	33	12	0.34	0.5
Hair Preparations (non-coloring)	***87***				
Hair Conditioners	2 (l.o.); 2 (r.o.)	NR	NR	NR	NR
Hair Sprays (aerosol fixatives)	8	NR	NR	NR	NR
Rinses (non-coloring)	1	NR	NR	NR	NR

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

	# of Uses			Max Conc of Use	
	RLD (2024)[14]	**VCRP (2023)[15]**	**VCRP (2002)[3]**	**% (2022)[16]**	**% (2003)[3]**
Shampoos (non-coloring)	7 (l.o.); 52 (r.o.)	NR	NR	0.24	NR
Tonics, Dressings, and Other Hair Grooming Aids	6	1	1	NR	NR
Other Hair Preparations	4 (l.o.); 6 (r.o.)	1	NR	NR	NR
Hair Coloring Preparations	***96***				
Hair Dyes and Colors (all types requiring caution statements and patch tests)	10	NR	NR	NR	NR
Hair Tints	44	NR	NR	NR	NR
Hair Rinses (coloring)	1 (r.o.)	NR	NR	NR	NR
Hair Color Sprays (aerosol)	14	NR	NR	NR	NR
Hair Bleaches	4	NR	NR	NR	NR
Eyelash and Eyebrow Dyes	6	NA	NR	NR	NR
Other Hair Coloring Preparation	17 (l.o.); 1 (r.o.)	NR	1	NR	NR
Makeup Preparations (not eye; not children's)	***9424***				
Blushers and Rouges (all types)	602	17	1	0.04 – 0.76	0.1 – 2
Face Powders	37	7	NR	1.4	0.4
Foundations	2978 (traditional application); 111 (airbrush application)	60	3	0.16 – 0.45	0.6 – 2
Leg and Body Paints	16 (traditional application)	2	NR	NR	NR
Lipsticks and Lip Glosses	4848	389	35	0.0064 – 3.9	0.03 - 2
Makeup Bases	127 (traditional application)	21	4	0.03 – 0.075	NR
Makeup Fixatives	71	1	2	NR	NR
Other Makeup Preparations	994 (l.o.); 28 (r.o.)	65	20	0.16 – 0.84	1
Makeup Preparations for Children (not eye)	***15***				
Children's Blushers and Rouges (All Types)	4	NA	NR	NR	NR
Children's Lipsticks and Lip Glosses	11	NA	NR	NR	NR
Manicuring Preparations	***665***				
Basecoats and Undercoats	11	2	NR	NR	NR
Cuticle Softeners	2	NR	NR	0.6	NR
Nail Creams and Lotions	1	NR	NR	0.15	NR
Nail Polishes and Enamels	553	1	NR	1.1	0.003
Nail Polish and Enamel Removers	107	NR	6	6	1
Other Manicuring Preparations	5	2	NR	NR	4
Oral Products	***1***				
Other Oral Products	1	NR	NR	NR	NR
Personal Cleanliness	***148***				
Bath Soaps and Body Washes	57	NR	NR	NR	NR
Deodorants (underarm)	3 (not spray); 8 (aerosol)	33	2	0.93 – 1.4 (aerosol)	0.2 – 5
Disposable Wipes	6	NA			
Other Personal Cleanliness Products	62 (l.o.); 12 (r.o.)	NR	26	NR	NR
Skin Care Preparations (creams, lotions, powder, and sprays)	***442***				
Cleansing (cold creams, cleansing lotions, liquids, and pads)	11	4	1	0.78 – 1.7	0.1
Face and Neck (excluding shaving preparations)	277 (l.o.); 19 (r.o.)	11	NR	3.8–6 (not spray)	NR
Body and Hand (excluding shaving preparations)	23 (l.o.); 5 (r.o.)	13	NR	0.05 (not spray)	NR
Foot Powders and Sprays	3	NR	NR	0.28	NR
Moisturizing	158	22	4	0.45 (not spray)	0.02 – 0.2
Night	7	4	1	17.9 (not spray)	NR
Paste Masks (mud packs)	4	NR	1	NR	0.3 - 2
Skin Fresheners	1	1	NR	NR	NR
Other Skin Care Preparations	48 (l.o.); 15 (r.o.)	17	NR	NR	NR
Suntan Preparations	***39***				
Suntan Gels, Creams, and Liquids	33	1	1	0.02–0.2 (not spray)	0.08 – 0.2
Indoor Tanning Preparations	4 (traditional application); 1 (spray application)	NR	NR	NR	NR
Other Suntan Preparations	2	NR	NR	NR	NR
Tattoo Preparations	***1***				
Temporary Tattoo Inks	1	NA	NR	NR	NR
Other Preparations (i.e., those preparations that do not fit another category)	***91***	NA	NA	NA	NA

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

Table 3. Repeated dose toxicity studies[6]

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results
ORAL						
Propylene Carbonate	Deionized water	Sprague-Dawley rats (5/sex/group)	28 d	0, 500, 1000, 2000, 3000, and 5000 mg/kg bw/d	OECD TG 407; treatment 5 d/wk; gavage administration	Post-dose salivation observed in some animals of all test doses. One male treated with 5000 mg/kg bw/d exhibited alopecia and scab formation on day 11-28. One female treated with 5000 mg/kg bw/d displayed decreased activity and lacrimation on day 9, another 5000 mg/kg bw/d-treated female displayed decreased activity on days 14-17. A statistically significant, dose-dependent increase in absolute ovary weights in females treated with 3000 and 5000 mg/kg bw/d was observed, compared to controls. Statistically significant increased relative liver weights were also observed in females treated with 1000 and 5000 mg/kg bw/d (compared to controls). Males treated with 5000 mg/kg bw/d displayed a statistically significant increase in testes weight (compared to controls). One female in the 3000 mg/kg bw/d group had a small left adrenal gland (50% smaller than right); one female from 5000 mg/kg bw/d group had hollow pelves of the left and right kidneys.
Propylene Carbonate	Deionized water	Sprague-Dawley rats (15/sex/group)	90 d	0, 1000, 3000, and 5000 mg/kg bw/d	OECD TG 408; treatment 5 d/wk; gavage administration; additional control and high dose groups served as recovery groups observed for 28 d after final dose administration; interim necropsies performed (day 30, day 90, or terminal necropsy (day 118))	Adverse effects that were observed at all dose levels include immediate post-dose salivation, rales, abnormal gait, abnormal stance, decreased activity, and dyspnea. Adverse effects observed at the mid-dose level include chromodacryorrhea, dislodged upper incisors, and increased blood phosphorous values (in males). Five high dose rats died during the study and 5 treated rats in recovery group died during test article administration (deaths were not considered to be test article related). A significant reduction of mean body weight, body weight gain, and food consumption observed in high-dose recovery males compared to recovery controls. A significant decrease in corpuscular volume was observed in high-dose males (compared to controls); significant increases in red blood cell counts, hematocrit, and hemoglobin observed in high-dose females (compared to controls). Clinical chemistry abnormalities observed 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[6]

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

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

Table 4. Dermal irritation and sensitization studies

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

Table 4. Dermal irritation and sensitization studies

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

SIOPT = single-insult occlusive patch test

Table 5. Ocular irritation studies

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

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

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