Safety Assessment of Dialkyl Carbonates as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	May 13, 2016
Panel Date:	June 6-7, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, Ivan Boyer, Ph.D., Senior Toxicologist, and Bart Heldreth, Ph.D., Chemist.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: May 13, 2016
Subject: Draft Report on Dialkyl Carbonates

A Scientific Literature Review (SLR) on Dialkyl Carbonate was announced on March 23, 2016. The ingredient use concentration data received from the Council prior to announcement of the SLR and unpublished data from industry have been incorporated. Comments on the SLR (now a Draft Report) that were received from the Council have been addressed.

Included in this package for your review is the Draft Report on Dialkyl Carbonates (*diacrb062016rep*), the CIR report history (*diacrb062016hist*), Literature search strategy (*diacrb062016strat*), Ingredient Data profile (*diacrb062016prof*), 2016 FDA VCRP data (*diacrb0620216FDAdata*), Use Concentration Data received from the Council (*diacrb062016data 1* and *diacrb062016data2*), Report Comments received from the Council (*diacrb062016pcpc1),* and unpublished data from industry (*diacrb06201data3).* The following data were received: (1) a sensitization and cutaneous compatibility study of a face and body oil containing 30.984% Dicaprylyl Carbonate and (2) an ocular and cutaneous acceptability study of a body, face, and hair oil containing 30.984% Dicaprylyl Carbonate.

After considering the data included in this safety assessment, the Panel will need to determine whether the data are sufficient to issue a tentative report with a conclusion of safe as used or safe with qualifications. If the data are not sufficient to reach a safety conclusion, the Panel should determine the additional data needed and issue an Insufficient Data Announcement.

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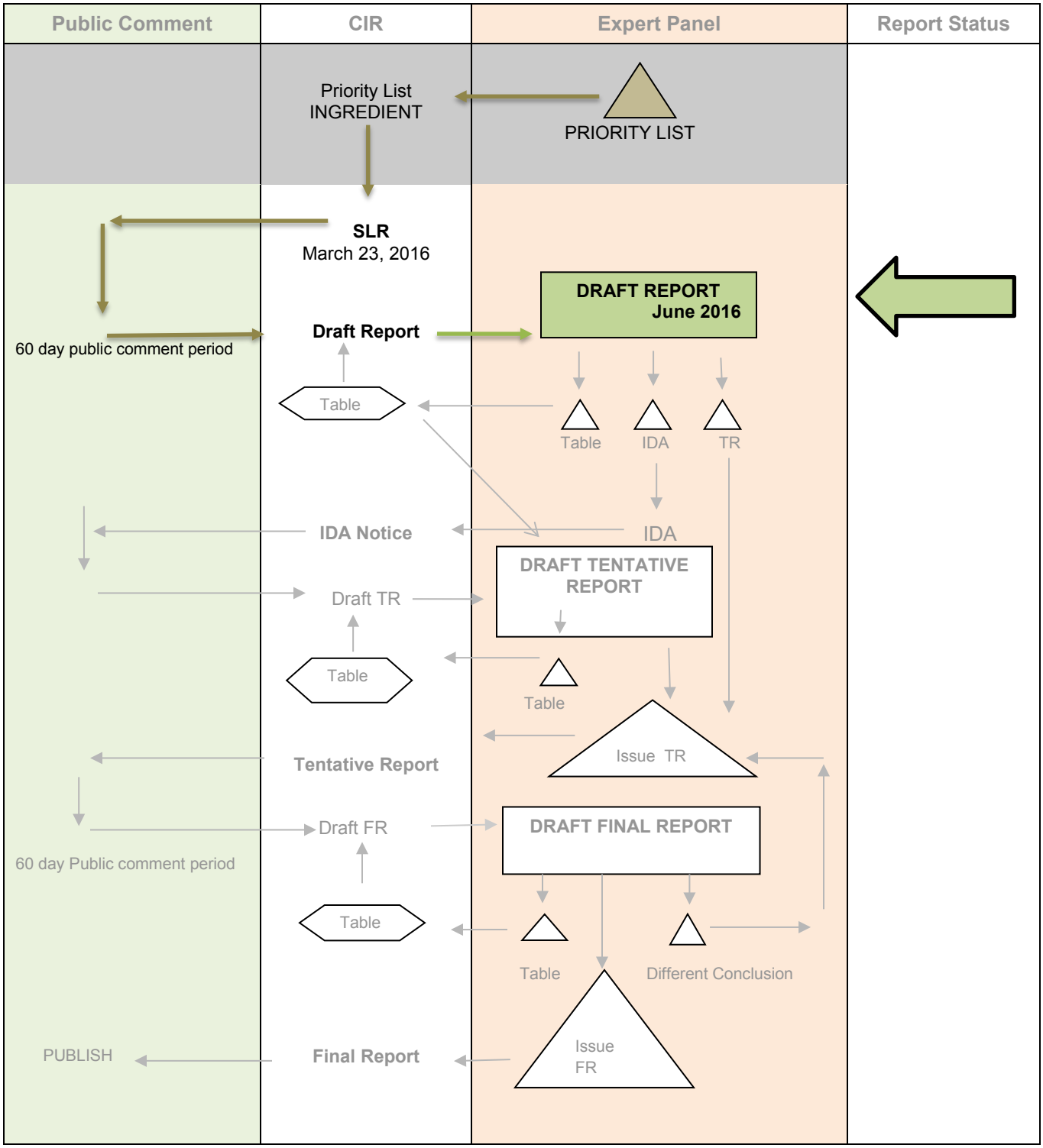
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Dialkyl Carbonates

MEETING June 2016



CIR History of:

Dialkyl Carbonates

The ScientificLiterature Review (SLR) was announced on 3-23-2016. Use concentration data were received from the Council prior to announcement of the SLR, and are included.

Draft Report, Teams/Panel: June 6-7, 2016

Report Comments and unpublished data were received, and have been incorporated. The following data were received: (1) a sensitization and cutaneous compatibility study of a face and body oil containing 30.984% Dicaprylyl Carbonate and (2) an ocular and cutaneous acceptability study of a body, face, and hair oil containing 30.984% Dicaprylyl Carbonate.

Dialkyl Carbonates Check List for June, 2016. Analyst – Wilbur Johnson																			
			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization				
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr.	Dermal Irr Human	Sensitization	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Dicaprylyl Carbonate				X		X		X				X	X	X	X	X		X		
Bis-Propylheptyl Carbonate																				
C14-15 Dialkyl Carbonate																				
Diethylhexyl Carbonate	X		X	X		X		X				X	X		X		X	X		
Dimethyl Carbonate			X	X		X	X	X		X		X	X		X		X	X		
Dipropyl Carbonate				X		X						X								

Literature Searches on Dialkyl Carbonates (1/5/2016)

SciFinder/PubMed Searches

Search Terms

Dicaprylyl Carbonate
+ (1680-31-5)
Bis-Propylheptyl Carbonate (No CAS No. in Dictionary)
C14-15 Dialkyl Carbonate (No CAS No. in Dictionary)
Diethylhexyl Carbonate (Check for Dioctyl Carbonate as synonym)
+ (14858-73-2)
Dimethyl Carbonate
+ (616-38-6)
Dipropyl Carbonate
+ (623-96-1)

Search Updates

Search updated on 4/28/2016

Safety Assessment of Dialkyl Carbonates as Used in Cosmetics

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INTRODUCTION

The safety of the following 6 dialkyl carbonates as used in cosmetics is reviewed in this safety assessment:

Dicaprylyl Carbonate
Bis-Propylheptyl Carbonate
C14-15 Dialkyl Carbonate
Diethylhexyl Carbonate
Dimethyl Carbonate
Dipropyl Carbonate

According to the *International Cosmetic Ingredient Dictionary and Handbook*, these ingredients function as skin conditioning agents in cosmetic products, except dimethyl carbonate, which functions as a fragrance ingredient, propellant, or solvent.[1] Dicaprylyl Carbonate is the only other ingredient that is reported to function as a solvent or conditioning agent in cosmetic products.

It is possible that alcohols previously reviewed by the Cosmetic Ingredient Review (CIR) may be considered relevant (as starting materials and potential metabolites) to this safety assessment of Dialkyl Carbonates. For example, data on propyl alcohol, included in the CIR safety assessment on Methyl Acetate, may be useful in the safety assessment of Dipropyl Carbonate.[2] Additionally, CIR has evaluated the safety of Methyl Alcohol in cosmetic products, which may be relevant for assessing the safety of Dimethyl Carbonate, and concluded that this ingredient is safe as used to denature alcohol used in cosmetic products.[3]

CHEMISTRY

Definition and General Characterization

The ingredients in this report are structurally related simple alkyl diesters of carbonic acid. Each ingredient comprises a carbonic acid residue diesterified with alkyl alcohols, which are as short as methanol (C1) to as long as pentadecyl alcohol (C15). For example, Dipropyl Carbonate is the apparent diesterification product of propanol and carbonic acid (Figure 1). The definitions of dialkyl carbonates are presented in Table 1.[1]

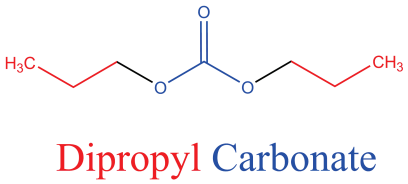


Figure1. Dipropyl Carbonate, an example dialkyl carbonate**.**

Chemical and Physical Properties

These low molecular weight (< 500 g/mol) ingredients vary from volatile liquids (Dimethyl carbonate can be used as a propellant) to low-temperature melting solids (the di-C15 ester component of C14-15 Dialkyl Carbonate melts at 39-41°C),[4] with variable solubilities in water that are inversely proportional to alkyl chain length. Other chemical and physical properties of these ingredients are presented in Table 2.

Method of Manufacture

Dimethyl Carbonate

Dimethyl Carbonate may be produced mostly by transesterification of methanol and propylene carbonate.[5]

Composition/Impurities

Decaprylyl Carbonate

A trade name material under which Dicaprylyl Carbonate is being marketed is 96.6% pure, and is made up of symmetric and unsymmetric carbonates (comprising C_6, C_8, and C_{10} chain lengths).[6] Neither hazardous nor non-hazardous impurities have been detected in this trade name material.

Dimethyl Carbonate

The results of a "typical analysis" of Dimethyl Carbonate were reported to be as follows: Dimethyl Carbonate (99.8 weight % minimum), water (0.1 weight % maximum), methanol (0.1 weight % maximum), chlorine (0.01 weight % maximum), aldehydes [as formaldehyde] (0.001 weight % maximum), and acids [as formic acid] (0.01 weight % maximum).[7]

USE

Cosmetic

The safety of the Dialkyl Carbonates included in this safety assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category. Collectively, the use frequency and use concentration data indicate that 3 of the 6 ingredients in this safety assessment are currently being used in cosmetic products (See Table 3). Based on these data, the following ingredients are not being used in cosmetics: Bis-Propylheptyl Carbonate, Dimethyl Carbonate, and Dipropyl Carbonate.

According to 2016 VCRP data, the greatest reported use frequency is for Dicaprylyl Carbonate (384 formulations, mostly leave-on products) (Table 3).[8] The results of a concentration of use survey conducted in 2015 indicate that Dicaprylyl Carbonate has the highest maximum concentration of use; it is used at concentrations up to 34.5% in leave-on products (eye shadow) (Table3).[9]

Cosmetic products containing Dialkyl Carbonates may be applied to the skin and hair or, incidentally, may come in contact with the eyes (e.g., Dicaprylyl Carbonate at maximum use concentrations up to 34.5% in eye area cosmetics) and mucous membranes (e.g., Dicaprylyl Carbonate at maximum use concentrations up to 2.7% in other personal cleanliness products). Additionally, Dicaprylyl Carbonate is being used in products that may result in incidental ingestion; however, use concentration data relating to this type of exposure were not received. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Dicaprylyl Carbonate is used in aerosol suntan products at maximum use concentrations up to 1.5% and in tonics, dressings and other hair grooming aids, which could possibly be sprayed, at concentrations up to 6%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm, compared with pump sprays.[10,11,12,13] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[10,11]

Noncosmetic

The Dialkyl Carbonates reviewed in this safety assessment do not appear on FDA's list of direct food additives or indirect food additives.

Dialkyl Carbonates

Dialkyl Carbonates are widely used as raw materials for the manufacture of agrochemicals, pharmaceuticals, and antioxidants, and as potential solvents for coating, adhesives and electrolytes in lithium ion batteries.[5]

Dimethyl Carbonate

Dimethyl Carbonate is a methylating agent in organic synthesis.[17,18,19,20,21,22,23,24]

TOXICOKINETIC STUDIES

Dermal Penetration

Diethyhexyl Carbonate

The dermal absorption of 99.9% Diethylhexyl Carbonate *in vitro* was evaluated according to OECD Guideline 428.[25] Human skin membranes (6 samples of abdominal skin, from females) were obtained, and split skin (~ 500 µm) consisting of the stratum corneum, epidermis, and part of the dermis was prepared. A punch (10 mm diameter) was used to produce skin slices for use in the flow-through diffusion cell, which consisted of a donor chamber, a receptor chamber, and receptor fluid. Six skin samples were used and 10 medium samples were collected during a 24-h period each. A validated GC-MSD method was used to measure Diethylhexyl Carbonate in the cell culture medium, making it possible to quantify Diethylhexyl Carbonate in the medium with precision and accuracy, down to a concentration of 10 µg/ml (corresponding to a detection limit of 0.025%). Diethylhexyl Carbonate (40 µl) was added to the donor chamber, and skin samples were exposed for 24 h. In all 60 samples, the concentration of Diethyl Carbonate was < 10 µg/ml. It was concluded that Diethylhexyl Carbonate could not be detected in the skin preparation samples for up to a skin exposure time of 24 h, and, therefore, that it is not expected to penetrate human skin.

Absorption, Distribution, Metabolism, and Excretion

In Vitro

Diethylhexyl Carbonate

An *in vitro* toxicokinetics study on Diethylhexyl Carbonate (25.77 ppm in acetonitrile) was performed using European Food Safety Authority (EFSA) Guidelines.[26] Hydrolysis in gastric fluid and in intestinal fluid simulants was evaluated. The results were reported as ~65% hydrolysis in gastric fluid and ~ 15% hydrolysis in intestinal fluid within 4 h. Additionally, these results were interpreted to mean that ~ 80% of ingested Diethyl Carbonate would be hydrolyzed within 4 h (hydrolysis in gastric fluid and intestinal fluid combined).

Animal

Dimethyl Carbonate

Dimethyl Carbonate is readily hydrolyzed by esterases to carbon dioxide and methanol in the environment and, presumably, in the body.[27] Methanol is metabolized to formaldehyde, which is then oxidized to formic acid; formic acid is then slowly metabolized to CO_2 and H_2O.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Dicaprylyl Carbonate

The acute dermal toxicity of a trade name material containing Dicapryl Carbonate was evaluated according to OECD Guideline 402 using groups of 10 (5 males, 5 females/group) Wistar rats.[6] The test material (dose = 5 g/kg) was applied under an occlusive dressing for 24 h, followed by a 14-day observation period. None of the animals died and there was no evidence of organ abnormalities at necropsy. The LD_{50} was determined to be >5 g/kg.

Diethylhexyl Carbonate

Groups of 10 Wistar rats (5 males, 5 females) were tested in an acute dermal toxicity study on Diethylhexyl Carbonate.[28] The test substance was applied (dose = 2 g/kg body weight) for 24 h to the skin of the dorsal area of the trunk using an occlusive patch. The area of exposure was defined as 10% of the total body surface. Dosing was followed by a 14-day observation period and gross necropsy examination. None of the animals died. Changes in skin at the application site were not observed, and there were no clinical signs of toxicity during the observation period. Body weight gain in all animals was within the expected range, and there were no test substance-related gross pathological changes. The LD_{50} was determined to be > 2 g/kg body weight.

Dimethyl Carbonate

The acute dermal toxicity of undiluted Dimethyl Carbonate was studied using 10 New Zealand white rabbits (5 males, 5 females).[29] The test substance (dose = 2 g/kg) was applied to a 240 cm^2 area of shaved skin for 24 h. A surgical dressing (covered with plastic film and secured with a lint-free cloth and an elastic adhesive bandage) remained on the test site during the application period. Dosing was followed by a 14-day observation period. None of the animals died. A decrease in mean body weight was observed during the study. Gross necropsy findings were normal in 8 rabbits. Multiple red foci on the lungs were observed in 2 rabbits, but these findings were not considered to be treatment-related. The acute dermal LD_{50} was reported to be > 2 g/kg body weight for Dimethyl Carbonate.

An acute dermal LD_{50} of > 2.5 g/kg was reported for Dimethyl Carbonate in a study involving cavies (in same rodent family [Caviidae] as guinea pigs; number and strain not stated).[23] Study details were not provided. An acute dermal LD_{50} of 2.5 g/kg was reported for Dimethyl Carbonate in a study involving rats.[30]

Dipropyl Carbonate

In a study involving rats (number and strain not stated), an acute dermal LD_{50} of 0.98 g/kg was reported for Dipropyl Carbonate (> 95%).[5,31] Study details were not included.

Oral

Dicaprylyl Carbonate

The acute oral toxicity of a trade name material containing Dicaprylyl Carbonate was evaluated according to OECD Guideline 401 using groups of 10 Sprague-Dawley rats (5 males, 5 females/group).[6] The test material was administered by gavage (in maize oil; dose = 5 g/kg), and dosing was followed by a 14-day observation period. No effect on body weight gain was observed and none of the animals died. There was no evidence of organ abnormalities at necropsy. The LD_{50} was determined to be > 5 g/kg.

Diethylhexyl Carbonate

Twelve Wistar rats (6 males, 6 females) were dosed orally, by gavage, with undiluted Diethylhexyl Carbonate at a single dose of 2 g/kg body weight.[32] The study was performed in accordance with OECD Guideline 423, and dosing was followed by a 14-day observation period and gross necropsy. None of the animals died and no clinical signs of toxicity appeared during the study. There were no test substance-related changes in body weight, and gross pathological examinations did not reveal any abnormal macroscopic findings. The LD_{50} was determined to be > 2 g/kg body weight.

Dimethyl Carbonate

The acute oral toxicity of Dimethyl Carbonate was evaluated according to OECD Guideline 401 using 10 Sprague-Dawley rats (5 males, 5 females).[33] The animals received a single oral dose of 5 g/kg body weight, followed by a 14-day observation period. Necropsy of surviving animals was performed. All animals gained weight, and none of the animals died during the study. Hypoactivity and ataxia were observed in 9 animals on the day of dosing, but there was no evidence of these signs by the second day after dosing. The following minor clinical signs were also observed: lacrimation, redness around the nose/eyes, discoloration (paws and around the mouth), and loss of hair under the chin. Gross necropsy findings were within normal limits in all animals. The LD_{50} was determined to be > 5 g/kg body weight in this study.

In an acute oral toxicity study involving rats (number and strain not stated), an LD_{50} of 13.8 g/kg was reported for Dimethyl Carbonate.[23,30] Study details were not provided. According to other acute oral toxicity studies, the acute oral LD_{50} of Dimethyl Carbonate in rats and mice (number of animals and strains not stated) ranges from 6.4 g/kg to 12.8 g/kg. The

exposure-related signs reported in these studies included weakness, ataxia with gasping, and unconsciousness. Additional study details were not presented.

Dipropyl Carbonate

The acute oral toxicity of Dipropyl Carbonate (> 95%) was evaluated in a study involving mice (number and strain not stated).[31] An LD_{50} of 0.3 g/kg was reported. Study details were not provided.

In a study involving rabbits (number and strain not stated), an acute oral LD_{50} of 3.2 g/kg was reported for Dipropyl Carbonate (> 95%).[31] Study details were not presented.

Inhalation

Dimethyl Carbonate

The acute inhalation toxicity of dimethyl Carbonate was evaluated according to OECD Guideline 403 using 10 Sprague-Dawley rats (5 males, 5 females).[34] The animals were exposed in a whole body inhalation chamber to Dimethyl Carbonate vapor for 4 h. The mean vapor concentration was 5.36 mg/l air minimum, and the minimum and maximum vapor concentrations were 4.56 and 5.77 mg/l, respectively. Exposure was followed by a 14-day observation period. Necropsy of surviving animals was performed. All of the animals gained weight and there were no deaths during the study. Redness around the nose was observed in one animal for approximately 1 h after exposure. This was the only adverse clinical sign that was observed during the study. Necropsy findings were within normal limits (7 animals necropsied). The LC_{50} for Dimethyl Carbonate was > 0.0054 g/l air.

In a study involving rats (number and strain not stated), an acute inhalation LC_{50} of 0.14 g/l was reported for Dimethyl Carbonate after an exposure period of 4 h.[23,30] Study details were not included. The results of another study (number of animals and strain not stated) indicated that exposure to Dimethyl Carbonate at a concentration of 8000 ppm for 2 h (4-h equivalence: 20.8 mg/l) caused gasping, loss of coordination, and death (in 2h) due to pulmonary edema.[35]

Short-Term Toxicity Studies

Animal

Dermal

Dimethyl Carbonate

Following a 28-day dermal exposure period (using a murine model), Dimethyl Carbonate caused a significant decrease in thymus weight at concentrations of ≥ 75%.[36] Effects on body weight or hematological parameters were not observed. Additional study results are included in the sections on Immunotoxicity and on Skin Irritation and Sensitization.

Oral

Diethylhexyl Carbonate

Short-term oral toxicity data on 2-ethylhexanol have been proposed for use in evaluating the short-term oral toxicity of Diethylhexyl Carbonate, and are included in a European Chemicals Agency (ECHA) registration dossier on Diethylhexyl Carbonate.[37] 2-ethylhexanol (in water) was administered orally (gavage) for 90 days to groups of 20 B6C3F1 mice (10 males, 10 females per group) at dose rates of 25, 50, 125, 250,or 500 mg/kg body weight/day according to OECD Guideline 408. The dose volume was 10 ml/kg body weight. Negative control animals were dosed with water. There were no test substance-related mortalities or clinical signs at any dose rate. Body weights were not reduced and there were no effects on clinicochemical and hematological parameters. The target organs were the liver and stomach, based on the significantly increased relative organ weights at termination of the test. Systemic effects were classified as minor, based on the lack of treatment-related findings in other organs, including the testes. A low incidence of local irritation effects in the forestomach was noted only at the highest administered dose (500 mg/kg/day). A NOEL (no observed effect level) of 125 mg/kg/day was reported for 2-ethylhexanol. A no observed adverse effect level (NOAEL) was estimated to be approximately 250 mg/kg/day based on study results.

Subchronic Toxicity Studies

Animal

Oral

Dicaprylyl Carbonate

A 13-week oral toxicity study on a trade name material containing Dicaprylyl Carbonate was performed according to OECD Guideline 407 using groups of 20 Sprague-Dawley rats (10 males, 10 females/group: 3 test and 1 control) and groups of 10 Sprague-Dawley rats (5 males, 5 females/group: 2 recovery groups).[6] The 3 test groups received oral doses (by gavage; corn oil vehicle) of 75, 250, and 1000 mg/kg/day, respectively, for 13 weeks consecutively, and the control group received corn oil according to the same procedure. The 2 recovery groups were high dose (1000 mg/kg/day) and control groups, respectively. For the recovery groups, the 13-week feeding period was followed by a 4-week treatment-free (recovery) period. There were no test material-related clinical observations or alterations in clinical chemistry parameters. However, variations in motor activity were observed in males dosed with 250 or 1000 mg/kg/day. All variations in clinical chemistry parameters were within historical control values. When compared to the control group, an increase in relative liver weights was observed in males of the 250 or 1000 mg/kg/day groups. In the 1000 mg/kg/day dose group, a reduction in relative liver weights was observed at the end of the recovery period. Decreased liver weights were reported for female rats of the 250 or 1000 mg/kg/day dose group; changes in liver weight were not observed at the end of the recovery period. Test material-related histopathological changes were not observed. The NOEL was determined to be ≥ 1000 mg/kg/day.

Dimethyl Carbonate

The subchronic oral toxicity of Dimethyl Carbonate was evaluated according to OECD Guideline 408 using groups of Sprague-Dawley rats (75 males, 75 females per group).[38] Dose rates of 1, 5, 50, and 500 mg/kg/day (in water) were administered orally (by gavage) once per day for 13 weeks. At the end of the exposure period, the animals were killed and subjected to gross necropsy and histopathological examinations. Three animals died during the study, but the deaths were not related to test substance administration. There were no test substance-related effects on body weight or body weight gain. The results of the following examinations were negative for test substance-related effects: ophthalmoscopic, hematology, clinical chemistry, urinalysis, gross necropsy, and histopathology. The oral administration of Dimethyl Carbonate was well-tolerated up to and including the highest dose rate of 500 mg/kg/day for 13 weeks. It was concluded that the no effect level in male and female rats was 500 mg/kg/day.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Diethylhexyl Carbonate

Data on the embryotoxicity/teratogenicity of 2-ethylhexanol have been proposed for use in evaluating this endpoint in the absence of data on Diethylhexyl Carbonate, and are included in an ECHA registration dossier on Diethylhexyl Carbonate.[39] Groups of 10 pregnant female Wistar rats were dosed orally with 2-ethylhexanol (in water containing 0.005% PEG-35 castor oil) at dose rates of 130, 650, and 1300 mg/kg body weight/day on gestation days 6 through 15 of gestation. The test protocol was conducted in accordance with OECD Guideline 414. The negative control group was dosed with vehicle only. The animals were killed on gestation day 20, and post-mortem examinations performed. Significant maternal toxicity was observed in the 1300 mg/kg/day group, and the following results were reported: discoloration of the liver and lung, pronounced clinical symptoms (nasal discharge, salivation, and CNS depression), reduced, food consumption, and body weight loss. Six of the 10 pregnant females dosed with 1300 mg/kg/day died. Slight maternal toxicity was noted at a dose of 650 mg/kg/day, but not at 130 mg/kg/day.

The following embryotoxic/teratogenic effects were reported after dosing with 1300 mg/kg/day: increased early resorptions, high postimplantation loss, markedly reduced fetal body weights, fetuses with a dilated renal pelvis and/or hydroureter, and increased incidences of skeletal malformations, variations, and retardations. In the 650 mg/kg/day dose group, slightly reduced mean fetal body weights and an increased frequency of fetuses with skeletal variations and retardations were observed. There were no adverse test substance-related effects on the dams or fetuses in the 130 mg/kg/day dose group.

After considering that maternal toxicity was most severe at 1300 mg/kg/day, marginal at 650 mg/kg/day, and nonexistent at 130 mg/kg/day, the NOAEL for this endpoint was determined to be 130 mg/kg/day. Because dose-dependent signs of embryotoxicity/fetotoxicity were observed in dams with signs of maternal toxicity at doses of 650 and 1300 mg/kg/day, the NOAEL was determined to be 130 mg/kg/day for this endpoint. The NOAEL for teratogenicity was determined to be 130 mg/kg/day because teratogenicity was observed only in fetuses from the highest dose group.

Inhalation

Dimethyl Carbonate

In a reproductive and developmental toxicity study, groups of 96 mated female CD-1 mice were exposed (6 h/day) to 300 ppm, 1000 ppm, or 3000 ppm Dimethyl Carbonate during gestation days 6 through 15 (organogenesis period).[27,35] Untreated mice served as controls. The females were killed on gestation day 18, after which fetuses from the first 30 to 32 pregnant dams were examined for external, visceral, and skeletal alterations. Exposure to 3000 ppm caused a significant reduction ($p < 0.01$) in maternal body weight and body weight gain. Food consumption was also significantly reduced after exposure to Dimethyl Carbonate at concentrations of 1000 ppm and 3000 ppm, indicating an adverse effect on the dams. Exposure to 3000 ppm also caused post-implantation loss, as evidenced by increased resorptions, increased number of stunted fetuses (< 1 g body weight), and altered sex ratio (fewer males surviving). A significant reduction ($p < 0.01$) in fetal body weight was also noted after exposure to 3000 ppm, indicating a gross adverse effect on the fetus.

The following fetal malformations were statistically significantly elevated after exposure to 3000 ppm: cleft palate ($p < 0.01$), microtia [small ear] ($p < 0.05$), low set ears ($p < 0.05$), imperforate anus ($p < 0.05$), and ectrodactyly ($p < 0.05$). An increase in multiple malformations of bones of the skull and in fused vertebral arches was also observed at this concentration. Increased skeletal variations at 3000 ppm included misshapen sternebrae (breastbones), rudimentary cervical ribs, and well-formed cervical or lumbar ribs. The effects on reproduction and fetal development, especially increased incidences of fetal malformations, were observed at a dose level at which general toxicity, such as decreased body weight gain in parental animals, was manifested. The NOAEL for maternal and developmental toxicity was 1000 ppm.[27,35]

GENOTOXICITY STUDIES

In Vitro

Dicaprylyl Carbonate

The genotoxicity of a trade name material containing Dicaprylyl Carbonate was evaluated in the Ames test (OECD Guideline 471), with and without metabolic activation, at doses up to 5000 µg/plate (vehicle = ethanol).[6] The following chemicals served as positive controls without metabolic activation: sodium azide, 9-aminoacridine, and 4-nitro-o-phenylenediamine. 2-Aminoanthracene served as the positive control with metabolic activation. The test material was not genotoxic, with or without metabolic activation, at doses up to 5000 µg/plate. The positive and negative controls performed as expected.

In the chromosomal aberration assay involving Chinese hamster V79 cells, the genotoxicity of the same trade name material was evaluated at concentrations up to 1000 µg/ml (without metabolic activation) and up to 2860 µg/ml (with metabolic activation).[6] Cultures were treated with the test material for 4 h. Ethyl methanesulfonate and cyclophosphamide served as positive controls without and with metabolic activation, respectively. Ethanol served as the negative control. Neither statistically significant/biologically relevant increases in chromosomal aberrations nor increases in the frequencies of polyploid metaphases were observed. It was concluded that the test material was not clastogenic with or without metabolic activation in this study.

Diethylhexyl Carbonate

Genotoxicity data on 2-ethylhexanol have been proposed for evaluating this endpoint in the absence of data on Diethylhexyl Carbonate, and are included in an ECHA registration dossier on Diethylhexyl Carbonate.[40] The genotoxicity of 2-ethylhexanol was evaluated in the L5178Y mouse lymphoma assay according to OECD Guideline 476. The chemical was tested on media containing mouse lymphoma L5178Y cells with and without metabolic activation. Test concentrations ranged from 0.013 µl/ml to 0.34 µl/ml. Ethyl methanesulfonate and dimethylbenzanthracene served as positive controls. 2-Ethylhexanol was not genotoxic over the range of concentrations tested. The 2 positive controls were genotoxic in this study.

Dimethyl Carbonate

The genotoxicity of Dimethyl Carbonate (in water) was evaluated according to OECD Guideline 476 using V79 Chinese hamster lung fibroblasts.[41] Dimethyl Carbonate was tested at concentrations up to 1000 µg/ml with and without metabolic activation. N-nitrosodimethylamine served as the positive control without metabolic activation, and ethyl methanesulfonate served as the positive control with metabolic activation. Hank's balanced salt solution supplemented with HEPES (HBSSH) served as the negative control. Dimethyl Carbonate was not genotoxic with or without metabolic activation. Results for the positive and negative controls were as expected.

In Vivo

Diethylhexyl Carbonate

Diethylhexyl Carbonate (in cottonseed oil) was evaluated for genotoxicity in the mouse micronucleus assay according to OECD Guideline 474.[42] Diethylhexyl Carbonate was tested at a dose rate of 2000 mg/kg body weight (dose volume = 10 ml/kg). Cyclophosphamide served as the positive control. Diethylhexyl Carbonate did not induce structural or numerical chromosome damage in the immature erythrocytes of the mouse. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow, and Diethyhexyl Carbonate was considered to be non-genotoxic. The positive control was genotoxic in this test.

CARCINOGENICITY STUDIES

Carcinogenicity data on Dialkyl Carbonates were not found in the published literature, and unpublished data were not provided.

OTHER RELEVANT STUDIES

Immunotoxicity

Dimethyl Carbonate

The immunotoxicity of Dimethyl Carbonate was evaluated using female BALB/c and $B_6C_3F_1$ mice in a series of studies.[36] In the hypersensitivity study, groups of 5 BALB/c mice were treated topically with acetone vehicle, increasing concentrations of Dimethyl Carbonate, or positive control substance [(30% α-hexylcinnamaldehyde (v/v; sensitization positive control) and 0.3% dinitrofluorobenzene (v/v; irritancy positive control)]. Topical applications were made to the dorsal surface of each ear once per day for 3 consecutive days.

In the immune phenotyping and hematology study, groups of 5 $B_6C_3F_1$ mice were exposed topically to acetone or increasing concentrations of Dimethyl Carbonate (50%, 75%, and 100%; volume = 50 µl). Topical applications were made to shaved skin of the back once per day for 28 consecutive days.

For an analysis of the IgM response to sheep red blood cells, $B_6C_3F_1$ mice (n = 6) were exposed topically to acetone or increasing concentrations of Dimethyl Carbonate (50%, 75%, and 100%; volume = 50 µl). Applications were made to shaved skin of the back for 28 consecutive days. Cyclophosphamide (20 mg/kg in isotonic saline) served as the positive control, and was injected intraperiotoneally.

Following a 28-day dermal exposure period, Dimethyl Carbonate caused a statistically significant decrease in thymus weight at concentrations $\geq$ 75%. Effects on the following parameters were not found: body weight, hematological parameters (erythrocytes, leukocytes, and their differentials), immune cell phenotyping (B-cells, T-cells, and T-cell subsets). The IgM antibody response to sheep red blood cells was reduced statistically significantly in the spleen, but not in the serum. These results indicate that dermal exposure to Dimethyl Carbonate was immunosuppressive in mice under the conditions of this study.[36]

DERMAL IRRITATION AND SENSITZATION STUDIES

Irritation

Animal

Dicaprylyl Carbonate

The skin irritation potential of a trade name material under which Dicaprylyl Carbonate is being marketed was evaluated according to OECD Guideline 404 using 6 New Zealand rabbits (3 males, 3 females).[6] The test material (0.5 ml) was applied for 4 h under a semi-occlusive patch to the skin of each animal. The dose per cm^2 was not stated. Patch removal was followed by a 21-day observation period. Very slight erythema was observed in all animals after 1 h of exposure, but persisted for up to 3 days in 2 animals only. Significant edema was not observed. However, scaling persisted in 3 animals. The trade name material was classified as slightly irritating to the skin of rabbits.

Diethylhexyl Carbonate

Three New Zealand White rabbits were used to evaluate the skin irritation potential of undiluted Diethylhexyl Carbonate.[43] The test substance was applied (0.5 ml under a semiocclusive patch) for 4 h to the left side of the back according to OECD Guideline 404. The surface area (cm^2) of the skin to which the material was applied was not stated. The untreated right side served as the control. Reactions were scored using the Draize system. Slight to well-defined erythema was observed in all animals 1 h after patch removal and persisted, unchanged or increasing in degree, up to day 4 or 5 after exposure. An erythema score of 3 was noted in one animal 24 h and 48 h after exposure and, in another animal, 72 h after exposure. A decrease in the severity of this reaction was observed over time, and the reversibility of the reaction was noted 7 and 8 after exposure. Very slight to slight edema was observed in animals between 1 h and 5 days after exposure. Slight eschar formation was observed in 1 animal on days 4 and 5 after exposure. The reactions observed in this study were fully reversible within 8 days after patch removal. Diethylhexyl Carbonate was classified as a skin irritant in this study.

Dimethyl Carbonate

The skin irritation potential of Dimethyl Carbonate (purity not stated) was evaluated according to OECD Guideline 404 using 3 female rabbits.[44] The test substance (0.5 ml) was applied to a 6 cm^2 area on the skin, and the application site was covered with a semiocclusive patch that was secured with a bandage around the trunk for 4 h. Untreated sites served as controls. Application was followed by a 72-h observation period, during which results were interpreted using the Draize method. Adverse reactions were not observed in the 3 rabbits tested. The primary dermal irritation index (PDII) was 0, and the test substance was classified as non-irritating.

Skin irritation potential was also evaluated in an acute dermal toxicity study of undiluted Dimethyl Carbonate involving 10 New Zealand white rabbits (5 males, 5 females).[29] No specific test guideline was followed, although it was noted that the methodology used in this study was broadly consistent with a limit test, as described in OECD Guideline 402. The test substance (dose = 2 g/kg) was applied to a 240 cm^2 area of shaved skin for 24 h. A surgical dressing (covered with plastic film and secured with a lint-free cloth and an elastic adhesive bandage) remained on the test site during the application period. Dermal irritation (edema and/or erythema at application site) was observed in all animals, and all reactions cleared within 5 days.

Human

Dicaprylyl Carbonate

The skin irritation potential of a trade name material containing Dicaprylyl Carbonate was evaluated using 20 male and female volunteers.[6] A single dose of the undiluted test material (70 µl) was applied to the back, under an occlusive dressing for 24 h. The dose per cm^2 was not stated. A sodium lauryl ether sulfate containing 2 ethoxylations in its chemical structure (1%) and sodium dodecyl sulfate (0.5%) served as the positive controls and demineralized water served as the negative control. The following skin reactions were used to determine skin tolerance to the test material: erythema, edema, scaling, and fissures. No reactions were observed after dermal application of the test material for 24 h. It was concluded that the test material was well-tolerated by human skin.

The cutaneous acceptability of a cosmetic investigational product (body, face, and hair oil) containing approximately 31% Dicaprylyl Carbonate was studied using 52 female subjects total.[51] During 4 weeks, the product was applied (once per day) on the face and body and twice per week on the hair. The first and last applications were performed at

the clinical unit. Values for the total number of applications (entire panel) were: face (1531 applications), body (1530 applications), and hair (508 applications). When the product was applied to the hair, the following reactions were reported: pruritus (1 subject), erythema (7 subjects), and desquamation (15 subjects). When the product was applied to the face or body, erythema was observed in 3 subjects and desquamation was observed in 7 subjects; irritatioin was observed only on the face.

Irritation and Sensitization

In Vitro

Dimethyl Carbonate

A combined local lymph node and irritancy assay was used to determine the irritation and sensitization potential of Dimethyl Carbonate at concentrations ranging from 50% to 100%.[36] Acetone served as the vehicle control. Dimethyl Carbonate was not found to be an irritant or sensitizer in the local lymph node assay (LLNA) in this test. Lymphocyte proliferation was not increased by exposure to Dimethyl Carbonate in this assay.

Animal

Dicaprylyl Carbonate

The Buehler test was used to evaluate the skin sensitization potential of a trade name material containing Dicaprylyl Carbonate.[6] During induction, the undiluted test material (0.2 ml in sesame oil) was applied for 6 h under an occlusive patch to the left flank of each of 20 female Dunkin-Hartley guinea pigs. The procedure was repeated on days 7 and 14. For each of the 3 induction applications, the dose per cm^2 was not stated. Ten guinea pigs treated with sesame oil served as controls. On day 28 (challenge), 0.2 ml of test material (concentration = 75%) was applied for 6 h under an occlusive patch to the right flank of test and control animals. Slight to moderate dermal reactions and scales were observed in some of the animals (number not stated) during induction. Signs of dermal irritation were not observed during the challenge phase. The test material was classified as a non-sensitizer.

Human

Dicaprylyl Carbonate

The skin irritation and sensitization potential of a cosmetic investigational product (liquid) containing approximately 31% Dicaprylyl Carbonate was evaluated using 108 male and female subjects in a human repeated insult patch test (HRIPT).[45] All 108 subjects were available for evaluation of primary cutaneous irritation and 104 subjects were available for evaluation of cumulative irritation and cutaneous sensitization. The product was applied to the back (0.02 ml over a 50 mm^2 surface) using a Finn Chamber (occlusive patch). The induction phase consisted of 9 applications spread out over a 3-week period. The duration of exposure was 48 ± 4 h for the 1^{st}, 2^{nd}, 4^{th}, 5^{th}, 7^{th} and 8^{th} induction applications, and the duration of exposure was 72 ± 4 h for weekends (3^{rd}, 6^{th}, and 9^{th} applications). The induction phase was followed by a 13-day (days 22 to 34) non-treatment period and then the challenge phase. Induction reactions were scored at 24 ± 3 h or 48 ± 4 h (for weekends) after patch removal. On day 35, a challenge patch was applied for 48 ± 4 h to 2 sites (virgin and previously treated). Challenge reactions were scored between 30 to 35 minutes and 48 ± 4 h after patch removal. Reactions were not observed during the induction or challenge phase, and the authors concluded that the product did not cause primary or cumulative irritation or cutaneous sensitization.

Sensitization

In Vitro

Diethylhexyl Carbonate

The skin sensitization potential of Diethylhexyl Carbonate [5%, 10%, and 15% w/v in acetone:olive oil (4:1 v/v)] was evaluated in the mouse LLNA according to OECD Guideline 429.[46] Hexyl cinnamic aldehyde served as the positive control. Diethylhexyl Carbonate was not a sensitizer when tested up to a concentration of 15%. The positive control had allergenic potency when tested at a concentration of 25% (w/w) in acetone: olive oil (4:1 v/v), but not when tested at a concentration of 15% (w/w) in acetone: olive oil (4:1 v/v).

Dimethyl Carbonate

A study was performed to evaluate the skin sensitization potential of Dimethyl Carbonate, using the modified Magnusson-Kligman method.[47] Two groups of 15 female Dunkin-Hartley guinea pigs were tested (1 group per test concentration). Induction exposure involved intradermal injection and epicutaneous (topical) applications in the scapular area (intradermal before topical patch application), and challenge exposure involved epicutaneous and semiocclusive applications to the back. Dimethyl Carbonate was tested (intradermal application) at a concentration of 100% or 25%. Intradermal application involved either no vehicle or 50:50 Freund's complete adjuvant (FCA), and topical (epicutaneous) induction involved no vehicle. At challenge (24 h patch application), Dimethyl Carbonate was tested at a concentration of 25% or 50% in ethanol and at a concentration of 100% (neat). Reactions were scored at 24 h and 48 h after patch removal. Reactions were not detected at challenge with either test concentration. Dimethyl Carbonate had no allergenic potential in the guinea pig and was classified as a non-sensitizer.

OCULAR IRRITATION STUDIES

In Vitro

Dimethyl Carbonate

In an *in vitro* assay (corneas – animal source not stated), Dimethyl Carbonate (solid form; no further details provided) was classified as a severe irritant.[48] Corneal opacity was not reported, but mean corneal swelling increased from a value of 16.6 at 1 h to 39.4 at 4 h. Slight pitting of the corneal epithelium was also observed. Additional study details were not included.

Animal

Dicaprylyl Carbonate

The ocular irritation potential of a trade name material containing Dicaprylyl Carbonate was evaluated according to OECD Guideline 405 using 6 New Zealand albino rabbits (3 males, 3 females).[6] The test material (0.1 ml) was instilled into the conjunctival sac of the left eye. Untreated eyes served as controls. Instillation of the test material was followed by a 3-day observation period. The test material was classified as slightly irritating to the eyes of rabbits.

Diethylhexyl Carbonate

In a study involving 3 New Zealand White rabbits, undiluted Diethylhexyl Carbonate (0.1 ml) was instilled into the conjunctival sac of the right eye according to OECD Guideline 405.[49] The eyes were not rinsed after instillation, and untreated eyes served as controls. Reactions were evaluated using the Draize scoring system. Slight or moderate redness and slight swelling of the conjunctivae were observed in all animals. At 1 h post-instillation, conjunctival redness, slight or moderate, was observed for up to 24 h post-instillation in 3 rabbits, and for up to 72 h post-instillation in 1 of these 3 rabbits. Ocular reactions were not found on day 4 of the study. Effects on the cornea were not detected. Diethylhexyl Carbonate was classified as non-irritating to the eyes of rabbits.

Dimethyl Carbonate

The ocular irritation potential of undiluted Dimethyl Carbonate was evaluated according to OECD Guideline 405 using 3 female New Zealand white rabbits.[50] The test substance (0.1 ml) was instilled into one eye of each animal, and eyes were not rinsed. Untreated eyes served as negative controls. The eyes were examined for signs of ocular irritation at 1 h, 24 h, 48 h, 72 h, and 7 days post-instillation, and reactions were scored using the Draize scale. Conjunctivitis [(moderate redness and discharge (grade 2) moderate-to-severe swelling (grades 2 to 3)] was observed in all treated eyes 1 h post-instillation. Neither corneal opacity nor iridial inflammation was observed at 1 h; however, 1 rabbit had slight corneal opacity and iridial inflammation 1 to 3 days post-instillation. The conjunctival irritation regressed and was slight on day 1 (all treated eyes). On day 7, all eyes appeared normal. Undiluted Dimethyl Carbonate was classified as mildly irritating to the eyes of rabbits.

Dipropyl Carbonate

Dipropyl Carbonate (> 95%, 100 mg) was instilled into the eyes of rabbits (number and strain not stated).[31] At 24 h, moderate ocular irritation was reported.

Human

Dicaprylyl Carbonate

The ocular irritation potential of a cosmetic investigational product (body, face, and hair oil) containing approximately 31% Dicaprylyl Carbonate was studied using 52 female subjects total.[51] Initially, the test groups were as follows: 20 subjects with sensitive eyes (Group 1), 11 subjects with non-sensitive eyes (Group 2), and 21 subjects wearing contact lenses (Group 3). During 4 weeks, the product was applied (once per day) on the face and body and twice per week on the hair. The first and last applications were performed at the clinical unit. At least 10 minutes after product application on the face and body, the following evaluations were performed by an ophthalmologist: ocular functional signs investigation of both eyes (Groups 1, 2, and 3), biomicroscopic examination of the ocular and peri-ocular structures on both eyes (Groups 1, 2, and 3), colorimetric examination of the cornea and conjunctiva of the right eye (Groups 1 and 2), tear film break-up time measurement on the right eye (Groups 1 and 2), and contact lenses examination of both eyes (Group 3). Values for the total number of applications (entire panel) were: face (1531 applications), body (1530 applications), and hair (508 applications). Ocular irritation was not observed during the study.

SUMMARY

The safety of the following 6 Dialkyl Carbonates as used in cosmetics is reviewed in this safety assessment: Dicaprylyl Carbonate, Bis-Propylheptyl Carbonate, C14-15 Dialkyl Carbonate, Diethylhexyl Carbonate, Dimethyl Carbonate, and Dipropyl Carbonate. These ingredients function mostly as skin conditioning agents in cosmetic products.

The results of what has been described as a typical analysis of Dimethyl Carbonate were as follows: Dimethyl Carbonate (99.8 weight % minimum), water (0.1 weight % maximum), methanol (0.1 weight % maximum), chlorine (0.01 weight % maximum), aldehydes [as formaldehyde] (0.001 weight % maximum), and acids [as formic acid] (0.01 weight % maximum).

Collectively, information supplied to FDA by industry as part of the VCRP and a survey of ingredient use concentrations conducted by the Council indicate that the following dialkyl carbonates are being used in cosmetic products: Dicaprylyl Carbonate, C14-15 Dialkyl Carbonate, and Diethylhexyl Carbonate. The highest use frequency is reported for Dicaprylyl Carbonate (384 uses). The Council survey data also indicate that Dialkyl Carbonates are being used in cosmetics at maximum ingredient use concentrations up to 34.5% (i.e., Dicaprylyl Carbonate in leave-on products [eye shadow]).

In an *in vitro* dermal penetration study involving human abdominal skin samples, Diethylhexyl Carbonate remained undetectable after 24 h of exposure. It was determined that that Diethylhexyl Carbonate would not be expected to penetrate human skin. The results of *in vitro* toxicokinetics study using gastric fluid and intestinal fluid simulants were interpreted as ~ 80% hydrolysis of Diethylhexyl Carbonate within 4 h (gastric and intestinal fluid combined).

Dimethyl Carbonate is readily hydrolyzed to carbon dioxide and methanol in the environment, and presumably, in the body, by esterases. Methanol is metabolized to formaldehyde, which is then further oxidized to formic acid.

In acute dermal toxicity studies, the following LD_{50} values have been reported for Dialkyl Carbonates: > 5 g/kg (Dicaprylyl Carbonate, rats), > 2 g/kg (Diethylhexyl Carbonate, rats), > 2 g/kg or 2.5 g/kg (Dimethyl Carbonate, rats), > 2.5 g/kg (Dimethyl Carbonate, cavies), and 0.98 g/kg (Dipropyl Carbonate, rats).

The following LD_{50} values have been reported for Dialkyl Carbonates in acute oral toxicity studies: > 5 g/kg (Dicaprylyl Carbonate), > 2 g/kg (Diethylhexyl Carbonate, rats), 13.8 g/kg (Dimethyl Carbonate, rats), > 5 g/kg (Dimethyl Carbonate, rats), 0.3 g/kg (Dipropyl Carbonate, mice), and 3.2 g/kg (Dipropyl Carbonate, rabbits). According to other acute oral toxicity studies, the acute oral LD_{50} value for Dimethyl Carbonate in rats and mice is between 6.4 g/kg and 12.8 g/kg.

In a study involving rats, an acute inhalation LC_{50} of 0.14 g/l was reported for Dimethyl Carbonate after an exposure period of 4 h. Following the same period of exposure, an LC_{50} of > 0.0054 g/l air was reported for Dimethyl Carbonate in another study involving rats.

Following a 28-day dermal exposure period (using a murine model), Dimethyl Carbonate caused a significant decrease in thymus weight and induced immune suppression at concentrations of ≥ 75%. Effects on body weight or hematological parameters were not observed.

In an ECHA registration dossier on Diethylhexyl Carbonate, short-term (90 days) oral toxicity data on 2-ethylhexanol were proposed for use in evaluating the safety of Diethylhexyl Carbonate. 2-Ethylhexanol was tested at doses up to 500 mg/kg/day in mice, and a NOEL of 125 mg/kg/day was reported. A NOAEL was not derived, but was estimated at 250 mg/kg/day.

In a 13-week toxicity study, Dimethyl Carbonate was administered orally to rats at doses up to 500 mg/kg/day. Results indicated that this dose was considered the no effect level. In another 13-week study, a trade name material under which Dicaprylyl Carbonate is being marketed was administered orally to rats at doses up to 1000 mg/kg/day. The NOEL was determined to be > 1000 mg/kg/day.

Embryotoxicity/teratogenicity data on 2-ethylhexanol in rats were proposed for use in evaluating the safety of Diethylhexyl Carbonate in an ECHA registration dossier. 2-Ethylhexanol was administered orally to rats at doses up to 13400 mg/kg/day on gestation days 6 through 15. Because dose-dependent signs of embryotoxicity/fetotoxicity were observed in dams with signs of maternal toxicity at doses of 650 and 1300 mg/kg/day, the NOAEL was determined to be 130 mg/kg/day for this endpoint. The NOAEL for teratogenicity was determined to be 1300 mg/kg/day because teratogenicity was observed only in fetuses from the highest dose group.

Dimethyl Carbonate was a reproductive and developmental toxicant in mice exposed (inhalation exposure) to a concentration of 3000 ppm. The increased incidences of fetal malformations were observed at a dose level at which general toxicity (i.e., decreased body weight gain) was observed in parental animals. The NOAEL for reproductive and developmental toxicity in this study was 1000 ppm.

In an ECHA registration dossier on Diethylhexyl Carbonate, *in vitro* genotoxicity data on 2-ethylhexanol were proposed for use in evaluating the safety of Diethylhexyl Carbonate. 2-ethylhexanol was not genotoxic in L5178Y mouse lymphoma cells, with or without metabolic activation, at concentrations up to 0.34 µl/ml. In another *in vitro* assay, Dimethyl Carbonate was not genotoxic in Chinese hamster lung fibroblasts, with or without metabolic activation, at concentrations up to 1000 µg/ml. In the *in vivo* mouse micronucleus assay, Diethylhexyl Carbonate was not genotoxic in bone marrow cells from mice after dosing with 2000 mg/kg. There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow cells.

The genotoxicity of a trade name material containing Dicaprylyl Carbonate was evaluated in the Ames test, with and without metabolic activation, at doses up to 5000 µg/plate. Results were negative. The same test material was not clastogenic in Chinese hamster V79 cells, with or without metabolic activation, when tested up to a dose of 1000 µg/ml (without metabolic activation) and up to a dose of 2860 µg/ml (with metabolic activation) in the chromosomal aberration assay.

Data relating to the carcinogenicity of the Dialkyl Carbonates that are used in cosmetic products were not found in the published literature.

In the local lymph node assay, Dimethyl Carbonate was not found to be an irritant or sensitizer when tested at concentrations ranging from 50% to 100%. Increases in lymphocyte proliferation were not identified in this assay. Dimethyl Carbonate (purity not stated) was non-irritating to the skin of all 3 rabbits tested; however, undiluted Dimethyl Carbonate was irritating to the skin of all 10 rabbits tested. All reactions had cleared within 5 days. When tested at concentrations of 25% and 50% during the challenge phase of the maximization test, Dimethyl Carbonate had no allergenic potential and was classified as a non-sensitizer.

The skin irritation potential of a trade name material under which Dicaprylyl Carbonate is being marketed was evaluated in a 4-h semi-occlusive patch test using 6 New Zealand rabbits. The test material was classified as slightly irritating to the skin of rabbits.

In a 4-h semi-occlusive patch test, Diethylhexyl Carbonate was irritating to the skin of all 3 rabbits tested. The skin irritation observed was fully reversible within 8 days after patch removal. In the LLNA, the skin sensitization potential of Diethylhexyl Carbonate was evaluated at concentrations up to 15% and results were negative.

The skin sensitization potential of a trade name material containing Dicaprylyl Carbonate was evaluated, and testing involved 3 induction applications and a single 6-h challenge (occlusive patch) in 20 guinea pigs. The test material was classified as a non-sensitizer. However, slight to moderate dermal reactions and scales were observed in some of the animals (number not stated) during induction. The skin irritation potential of the same test material was evaluated in a 24-h occlusive patch test using 20 male and female volunteers. The test material was well-tolerated by human skin.

The skin irritation and sensitization potential of a cosmetic investigational product (liquid) containing 30.984% Dicaprylyl Carbonate was evaluated in an HRIPT involving 108 male and female subjects. The product did not cause primary or cumulative irritation or cutaneous sensitization.

In an *in vitro* assay (corneas – animal source not stated), Dimethyl Carbonate (solid) was classified as a severe irritant. Undiluted Dimethyl Carbonate was mildly irritating to the eyes of all 3 rabbits; all eyes appeared normal on day 7 post-instillation.

After undiluted Diethylhexyl Carbonate was instilled into the eyes of 3 rabbits, ocular irritation was observed at 24 h and 72 h post-instillation, but not on day 4. Diethylhexyl Carbonate was classified as non-irritating to the eyes of rabbits (number not stated). Dipropyl Carbonate (> 95%) was classified as a moderate ocular irritant in rabbits. The ocular irritation potential of a trade name material under which Dicaprylyl Carbonate is being marketed was evaluated using 6 New Zealand albino rabbits. The test material was classified as slightly irritating to the eyes of rabbits.

The ocular and cutaneous acceptability of a cosmetic investigational product (body, face, and hair oil) containing 30.984% Dicaprylyl Carbonate was studied using 52 female subjects total. Of the 52 subjects, 47 cases were considered valid. During 4 weeks, the product was applied (once per day) on the face and body and twice per week on the hair. Ocular irritation was not observed during the study.

Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.[1]

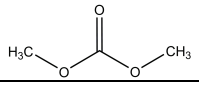
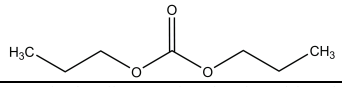
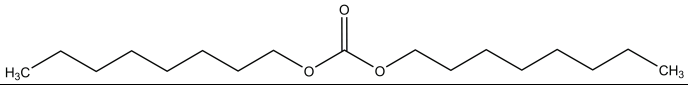
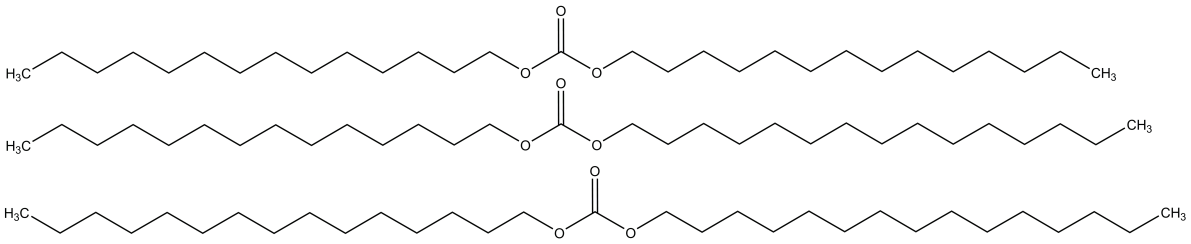
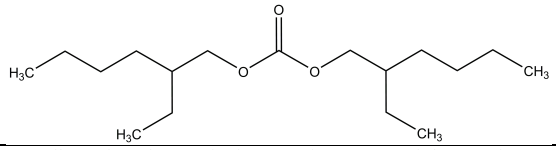
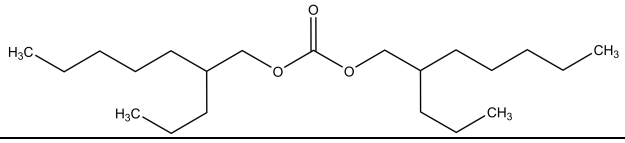
Ingredient CAS No.	Definition & Structure	Function
Dimethyl Carbonate 616-38-6	Dimethyl Carbonate is the organic compound that conforms to the formula: 	Fragrance Ingredients; Propellants; Solvents
Dipropyl Carbonate 623-96-1	Dipropyl Carbonate is the organic compound that conforms to the formula: 	Skin-Conditioning Agents - Miscellaneous
Dicaprylyl Carbonate 1680-31-5	Dicaprylyl Carbonate is the diester of carbonic acid and caprylyl alcohol. It conforms to the formula: 	Skin-Conditioning Agents - Emollient; Solvents
C14-15 Dialkyl Carbonate [153821-35-3 Di-C14 145197-00-8 Di-C15]	C14-15 Dialkyl Carbonate is the organic compound that conforms generally to the formula: 	Skin-Conditioning Agents - Emollient
Diethylhexyl Carbonate 14858-73-2	Diethylhexyl Carbonate is the organic compound that conforms to the formula: 	Skin-Conditioning Agents - Emollient
Bis-Propylheptyl Carbonate [1238449-42-7]	Bis-Propylheptyl Carbonate is the organic compound that conforms to the formula: 	Skin-Conditioning Agents - Emollient

Table 2. Properties of Dialkyl Carbonates

Property	Value	Background Information
	Dimethyl Carbonate	
Form/Odor	Smells like methanol.[23]	Short-chain symmetrical Dialkyl Carbonates are colorless, transparent liquids with a pleasant odor.[5]
Viscosity	0.625 cP @ 20°C.[30]	
Molecular Mass	90.08.[5,30]	
Solubility	139 g/l in water.[5] 13.9 g/100 g.[30]	The solubility of Dialkyl Carbonates in different media depends on the length of the carbon chain. Most are soluble in water and dissolve easily in polar organic solvents, such as ethanol.[5] Dimethyl Carbonate is miscible with ethanol, ethers, esters, and ketones.[30]
Melting Point	4.6˚C.[5,30]	
Boiling Point	90.3 ˚C.[5,30]	
Density	1.069 g/cm^3.[5] 1.07 g/cm^3.[30]	
Reactivity		Dimethyl Carbonate has 3 reactive centers that can interact with nucleophiles: the carbonyl and 2 methyl groups.[52] The carbonyl group is the harder electrophile (due to its polarized positive charge and sp^2 hybridization), and the 2 methyl groups represent softer electrophiles (due to their sp^3 orbital and their saturated carbon atom, which has a weaker positive charge). Dimethyl Carbonate behaves as a methylating agent toward substrates with acidic hydrogens.[7]
Octanol/Water Partition Coefficient (log Pow)		0.354 at 20˚C.[53]
	Dipropyl Carbonate	
Form	Yellow liquid.[54]	
Molecular Mass	146.19.[5]	
Solubility	4.1 g/l in water.[5]	
Melting Point	- 41˚C.[5]	
Boiling Point	168.2˚C.[5] 167°C to 168°C.[54]	
	Dicaprylyl Carbonate	
Form	White liquid.[6]	Stable and non-reactive. Can decompose to carbon dioxide, carbon monoxide, and sulfur dioxide when mixed with strong acids and oxidizing agents or when exposed to fire.[6]
Solubility	0.1 mg/l in water.[6]	
Melting Point	-22˚C.[6]	
Boiling Point	330˚C.[6]	
Specific Gravity	0.8906 ± 0.00002 at 20˚C.[6] 4.2 ± 0.2 at 23.5˚C.[6]	
Octanol/Water Partition Coefficient (log Pow)		

	C14-15 Dialkyl Carbonate
Molecular Weight (g/mol)	474.78 – 482.83.[57]
	Diethylhexyl Carbonate
Form	Clear, colorless liquid.[55]
Solubility	< 0.03 mg/l in water.[56]
Melting Point	< -100°C.[55]
Boiling Point	317°C.[55]
Density	0.9 g/cm^3 at 20°C.[55]
Octanol/Water Partition Coefficient (log Pow)	>4.1 at 21°C.[56]
	Bis-Propylheptyl Carbonate
Molecular Weight (g/mol)	342.56.[57]

Table 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[8,9]

	Dicaprylyl Carbonate		C14-15 Dialkyl Carbonate		Diethylhexyl Carbonate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	384	0.3-34.5	NR	2	16	2-7.5
Duration of Use						
Leave-On	334	0.34-34.5	NR	NR	16	2-7.5
Rinse off	48	0.3-4	NR	2	NR	NR
Diluted for (bath) Use	2	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	31	2-34.5	NR	NR	4	NR
Incidental Ingestion	13	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	10*	1.5; 2-6*	NR	NR	NR	NR
Incidental Inhalation- Powders	2	0.34-31**	NR	NR	NR	NR
Dermal Contact	351	0.34-34.5	NR	2	16	2-7.5
Deodorant (underarm)	6	NR	NR	NR	NR	NR
Hair - Non-Coloring	18	0.3-2.9	NR	NR	NR	NR
Hair-Coloring	2	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	19	2.7	NR	NR	NR	NR
Baby Products	1	NR	NR	NR	NR	NR

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted (for bath) Product Uses.
*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.
** It is possible that these products may be powders, but it is not specified whether the reported uses are powders.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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2016 FDA VCRP Data

Dicaprylyl Carbonate

01B - Baby Lotions, Oils, Powders, and Creams	1
02A - Bath Oils, Tablets, and Salts	2
03B - Eyeliner	3
03C - Eye Shadow	3
03D - Eye Lotion	15
03E - Eye Makeup Remover	1
03G - Other Eye Makeup Preparations	9
04E - Other Fragrance Preparation	3
05A - Hair Conditioner	7
05F - Shampoos (non-coloring)	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	4
05I - Other Hair Preparations	6
06C - Hair Rinses (coloring)	1
06H - Other Hair Coloring Preparation	1
07A - Blushers (all types)	4
07B - Face Powders	1
07C - Foundations	14
07E - Lipstick	13
07F - Makeup Bases	2
07I - Other Makeup Preparations	2
10A - Bath Soaps and Detergents	1
10B - Deodorants (underarm)	6
10E - Other Personal Cleanliness Products	3
11A - Aftershave Lotion	13
11G - Other Shaving Preparation Products	1
12A - Cleansing	27
12C - Face and Neck (exc shave)	64
12D - Body and Hand (exc shave)	51
12F - Moisturizing	60
12G - Night	29
12H - Paste Masks (mud packs)	5
12J - Other Skin Care Preps	28
13A - Suntan Gels, Creams, and Liquids	2
13B - Indoor Tanning Preparations	1
Total	**384**

Bis-Propylheptyl Carbonate - No FDA Data

C14-15 Dialkyl Carbonate - No FDA Data

Diethylhexyl Carbonate

03D - Eye Lotion	2
03G - Other Eye Makeup Preparations	2
07C - Foundations	4
07F - Makeup Bases	2

12C - Face and Neck (exc shave)	2
12D - Body and Hand (exc shave)	3
13B - Indoor Tanning Preparations	1
Total	**16**

Dimethyl Carbonate - No FDA Data

Dipropyl Carbonate - No FDA Data

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 9, 2015

SUBJECT: Concentration of Use Information: Dialkyl Carbonates

Concentration of Use by FDA Product Category – Dialkyl Carbonates*

Dicaprylyl Carbonate | C14-15 Dialkyl Carbonate | Dimethyl Carbonate
Bis-Propylheptyl Carbonate | Diethylhexyl Carbonate | Dipropyl Carbonate

Ingredient	Product Category	Maximum Concentration of Use
Dicaprylyl Carbonate	Eyeliner 3B	3-21%
Dicaprylyl Carbonate	Eye shadow 3C	3-34.5%
Dicaprylyl Carbonate	Eye lotion 3D	2-5%
Dicaprylyl Carbonate	Eye makeup remover 3E	4%
Dicaprylyl Carbonate	Other fragrance preparations 4E	31%
Dicaprylyl Carbonate	Hair conditioners 5A	0.3-2.5%
Dicaprylyl Carbonate	Shampoos (noncoloring) 5F	2.5%
Dicaprylyl Carbonate	Tonics, dressings and other hair grooming aids Not spray 5G	2-6% 2.9%
Dicaprylyl Carbonate	Blushers 7A	3.1-12.3%
Dicaprylyl Carbonate	Foundations 7C	5-15.3%
Dicaprylyl Carbonate	Makeup bases 7F	6%
Dicaprylyl Carbonate	Other makeup preparations 7I	11.5-21.5%
Dicaprylyl Carbonate	Other personal cleanliness products 10E	2.7%
Dicaprylyl Carbonate	Aftershave lotions 11A	2-5%
Dicaprylyl Carbonate	Skin cleansing (cold creams, cleansing lotions, liquids and pads) 12A	1-2.4%
Dicaprylyl Carbonate	Face and neck products 12C Not spray	 0.34-30%
Dicaprylyl Carbonate	Body and hand products 12D Not spray	 2-31%
Dicaprylyl Carbonate	Moisturizing products 12F Not spray	 1.5-31%
Dicaprylyl Carbonate	Night products 12G Not spray	 5.3-30%
Dicaprylyl Carbonate	Other skin care preparations 12J	1-3%
Dicaprylyl Carbonate	Suntan products 13A Not spray Aerosol	 2-7% 1.5%
C14-15 Dialkyl Carbonate	Skin cleansing (cold creams, cleansing lotions, liquids and pads) 12A	2%
Diethylhexyl Carbonate	Foundations 7C	2%
Diethylhexyl Carbonate	Moisturizing products 12F Not spray	 2.5%
Diethylhexyl Carbonate	Suntan products 13A Not spray	 7.5%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2015
Table prepared October 8, 2015

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 18, 2016

SUBJECT: Dicaprylyl Carbonate

I.E.C. Bulgarie. 2009. Sensitisation and cutaneous compatibility study face and body oil containing 30.984% Dicaprylyl Carbonate.

Peritesco. 2009. Ocular and cutaneous acceptability study of a body, face and hair oil (containing 30.984% Dicaprylyl Carbonate) during 4 weeks under ophthalmological and dermatological supervision.

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I.E.C. BULGARIE

REPORT: SENSITISATION AND CUTANEOUS COMPATIBILITY STUDY

DT033593

VERIFICATION OF THE ABSENCE OF SENSITISING POTENTIAL AND OF THE GOOD CUTANEOUS COMPATIBILITY OF A COSMETIC INVESTIGATIONAL PRODUCT, BY REPEATED EPICUTANEOUS APPLICATIONS UNDER OCCLUSIVE PATCH, IN 108 (OR 104) HEALTHY ADULT SUBJECTS
(modified Marzulli and Maibach method)

INVESTIGATIONAL PRODUCT	Dicaprylyl Carbonate 30.984% Face and Body Oil- batch n° F1 of 18/05/2009
PROTOCOLS	Specific N° B090821PE of 15 June 2009 and amendment n° 1 of 6 July 2009 refer to Standard N° EN_P_STD_CLITP_5021_01, of20 January 2005
REPORT	N° B090821RD10 -version 1 of 2 November 2009
BEGINNING OF THE OBSERVATIONS	23 June 2009
END OF OBSERVATIONS	5 August 2009

SAFETY ASSESSOR	TECHNICAL AND SCIENTIFIC MANAGER	DERMATOLOGISTS
[redacted]	Mrs. M. VASSILEVA Post-Graduate in Life and Health Sciences I.E.C. Bulgarie Lozenetz - 16A, Kichinev Street 1407 SOFIA- BULGARIA	-Dr. Z. PANOVA, M.D. *(Investigator)* -Dr. G. BOCHEVA, M.D., Investigating Laboratory: I.E.C. Bulgarie Lozenetz - 16A, Kichinev Street 1407 SOFIA- BULGARIA

Document of 61 pages

AUTHENTICATION

The study subject of the present report was conducted under my responsibility, in compliance with standard and specific study protocols, in accordance with I.E.C. Standard Operating Procedures and in the spirit of the general principles of the Good Clinical Practices (ICH topic E6-CPMPIICH/135/95).

I assume the responsibility of the validity of all raw data obtained during this study and mentioned in the present report.

Dr. Zoya PANOVA,
Dermatologist Investigator

I have read this report, I certify that these data are an accurate reflection of the results obtained and I agree with its content.

02.11.09

Margarita VASSILEVA
Technical and Scientific Manager

PERSONNEL INVOLVED IN THE REALISATION OF THE STUDY

(for I.E.C. France)

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Independent Ethical Committee

Names: -Mr. G. VELEY, Executive Director I.E.C. Bulgarie
- Mrs. M. VASSILEVA, Post-Graduate in Life and Health Sciences, Technical and Scientific Manager I.E.C. Bulgarie
- Dr. E. LICHEVA, Dermatologist, Clinical Investigator, Consultant I.E.C. Bulgarie
-Mr. G. STOIMENOV*, Law teacher in the "New Bulgarian University", European Law, Protection of the Human rights
-Prof. R. YANKOVA*, M.D., Ph.D, Chief of Dermatology and Allergology Department, University of Medicine "St. George" Plodiv, Bulgaria
- Dr. G. MINCHEYA*, M.D., Allergologist-Dermatologist (Allergology test with cosmetic products and detergents), Dermatology & Venerology Dispensary, Sofia, Bulgaria

**Members independent from the Investigating Laboratory and from the Study Monitor (Sponsor), who vote/give their opinion about the study.*

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ENGLISH SUMMARY OF THE REPORT

SPONSOR: [redacted]

INVESTIGATIONAL PRODUCT: Dicaprylyl Carbonate 30.984% Face and Body Oil- batch n° F1 of 18/05/2009)

DT033593

SENSITISATION AND CUTANEOUS COMPATIBILITY STUDY

VERIFICATION OF THE ABSENCE OF SENSITISING POTENTIAL AND OF THE GOOD CUTANEOUS COMPATIBILITY OF A COSMETIC INVESTIGATIONAL PRODUCT, BY REPEATED EPICUTANEOUS APPLICATIONS UNDER OCCLUSIVE PATCH, IN 108 (OR 104) HEALTHY ADULT SUBJECTS
(modified Marzulli and Maibach method)

INTRODUCTION	The study consists in the application of the investigational product under maximized application conditions according to the modified Marzulli and Maibach method. It is carried out on cosmetic product whose safety had been assured by a toxicologist, with the aim to further confirm safety of this product which will be used by a large number of consumers under normal and reasonably foreseeable use conditions.
STUDY OBJECTIVE	To confirm that the repeated application, under patch, of investigational product, on the subject's back, does not induce an allergic reaction and to evaluate its good cutaneous compatibility.
STUDY RELEVANCE	Cutaneous allergy is an individual phenomenon, of immune origin, of which setting off activating 3 phases (penetration of the foreign substance in the skin and forming of the allergen; development of the immune reaction; activating of the reaction, by a new application of the allergenic molecule to the skin). These 3 phases are thus required to check, in 50 or 100 subjects, the absence of sensitising potential of an investigational product, and are the basis of the method described by Marzulli and Maibach *(protocol in conformity to note dated 4 August 1997 of the French "Repression des Fraudes" to the "Federation Franc;aise des Industries de la Parfumerie").*

INCLUSION CRITERIA SPECIFIC TO THE STUDY *(in addition to the criteria given in the standard study protocol)*	To be eligible, each subject must satisfy all the criteria written in the standard study protocol [redacted] N°: EN_P_STD_CLITP_5021_01, of 20 January 2005 and the specific following ones: . *Number of subjects:* 100 subjects divided in two panels of 50 subjects receiving 14 investigational products for one panel and 13 investigational products for the other one (the product distribution being indicated in the application scheme of the Case Report Form). . *Selection of subjects:* exclusive selection of 100 valid cases (a valid case will be defined as a subject who has completed a full procedure (9 applications and 9 readings during the induction phase followed by a double application (induction and virgin sites) and 2 readings during the challenge phase [or more if this is necessary in order to fully evaluate observed reaction]). However, a subject who has presented with significant reactions (moderate erythema and/or infiltration and/or papules and/or vesicles) twice during the induction phase, inducing a stop of application, but who received the challenge phase application after decision of the Dermatologist Investigator and the Sponsor, will be considered as a valid case even though he had not followed the previous procedure. . *Sex:* female and male . *Age:* 18 to 70 years old (the 60-70 age bracket should not exceed 10% of the total number of subjects) . *Origin:* Caucasian . *Phototypes:* I, II or III . *Healthy subjects:* 100% without "atopic" background.
NON-INCLUSION CRITERIA SPECIFIC TO THE STUDY *(in addition to the criteria given in the standard study protocol)*	To be eligible, each subject must not meet any criterion written in the standard protocol cited above.
METHODOLOGY	-Modes of **application:** . *area:* back . *quantity:* 0.02 ml over a 50 mm² surface (occlusive patch: Small Finn Chambers on Scanpor) or 0.2 ml over a 4 cm² surface (semi-occlusive patch: Brady, U.S.A.), in case of reaction. . *conditions of application:* the investigational product, being under a liquid form was put onto a disc of filter paper (7 mm in diameter) previously inserted into the cupule. . *frequency and duration:* . induction phase: 9 applications spread out over 3 weeks as follows: 1st week: Day 0 (Tuesday: 1st application), Day 2 (Thursday), Day 4 (Saturday), 2nd week: Day 7 (Tuesday), Day 9 (Thursday), Day 11 (Saturday), 3rd week: Day 14 (Tuesday), Day 16 (Thursday), Day 18 (Saturday) Duration of exposure: 48±4 hours for the 1st,2nd,4th,5th,7th and 8th applications or 72 ± 4 hours for the week-ends (3rd, 6th and 9th applications). . rest phase: the subjects are not submitted to any application from Day 22 (Wednesday) to Day 34 (Monday) inclusive, i.e. for a 13-day period. . challenge phase: single application on 2 sites (virgin and induced sites) on Day 35 (Tuesday) for 48 ± 4 hours. N.B.: the patches are removed by the Laboratory staff.

METHODOLOGY *(con't)*	**- Modes of evaluation:** - *Clinical observations:* readings performed, according to the Sponsor's specificities (D2, D35, D37 and D39), by the Dermatologist Investigator: . *Induction phase:* 24 ± 3 hours or 48 ± 4 hours (for the weekends) after removal of the patches . *"challenge" phase:* between 30 to 35 min and 48 ± 4 hours after removal of the patches or more if this is necessary in order to fully evaluate observed reactions. - *Grading,* according to a given numerical scale (irritation scale: 0 to 4 & scale of the International Contact Dermatitis Research Group (I.C.D.R.G.): 0 to 3 [+++]).
ANALYSIS OF THE RESULTS AND EVALUATION CRITERIA	-Determination of the Mean Irritation Index (M.I.I): equal to the sum of the quotations of the 9 readings of the induction phase divided by the number of subjects and of readings performed. -Interpretation of the results obtained, under the experimental conditions adopted: . **for cumulative irritation:** arbitrary classification ("non-irritating" to "severely irritating");

M.I.I	Classification of the investigational product
Lower than 0.25	Non-irritant
0.25 to 1 not included	Slightly irritant
1 to 2 not included	Moderately irritant
2 to 3 not included	Very irritant
3 to 4	Severely irritant

. for sensitizing potential:

An erythema, of intensity higher than or equal to 2 during the "challenge" phase, with or without palpable lesions, must be evaluated in the following days to determine if the reaction decreases or increases in order to precise if the reaction observed is of allergical or irritative type. A quick decrease of the reaction indicates an irritation (decrescendo reaction). A reaction with presence of infiltration/oedema, which persists and/or which increases within time generally indicates a reaction of allergical type, and additional studies ("rechallenge" and/or R.O.A.T.: Repeated Open Application Test) could be performed 3 to 6 weeks after the first appearance of the challenge reaction and after all reactions have ceased.

. also on the base of the type of investigational product and the I.E.C. statistics established on about 3,900 investigational products tested at I.E.C. Bulgarie between 2002 and 2007 (positionning of cumulative irritation and/or sensitisation in comparison of investigational products of the same type).

RESULTS AND CONCLUSION

STUDIED POPULATION

Number of subjects recruited	146
Number of subjects who came to I.E.C.	124
Number of subjects included by the Dermatologist Investigator	111
Number of subjects discontinued from the study	7
Number of subjects for the analysis of the results . for the evaluation of Primary Cutaneous Irritation . for the evaluation of Cumulative Irritation . for the evaluation of Cutaneous Sensitization	 108 104 104

The physical characteristics of the subjects are summarized in the following table:

Subjects	Primary Cutaneous Irritation	Cumulative Irritation	Cutaneous Sensitization
Number	108	104	104
Females	102	98	98
Males	6	6	6
Age minimum (y.o.)	18	18	18
Age maximum (y.o.)	69	69	69

RESULTS

Percentage of subjects having presented with one or several well visible to severe irritation reactions (score2), during the induction	0%
Mean Irritation Index (M.I.I.) of the induction Classification of the investigational product	0 ✓ non-irritant: M.I.I. < 0.25 o slightly irritant: M.I.I. [0.25 - 1[o moderately irritant: M.I.I. [1 - 2[o very irritant: M.I.I. [2 - 3[o severely irritant: M.I.I.[3- 4[
Percentage of the sensitisation reactions observed	0%
Reactions considered as serious adverse events linked to the investigational product	0%

CONCLUSION

In conclusion and given the results obtained under the experimental conditions adopted, the single and repeated epicutaneous applications of the investigational product designated as " (Dicaprylyl Carbonate 30.984% Face and Body Oil- batch no FI of 18/05/2009)", under occlusive patch, in the healthy adult subject, did not provoke any primary or cumulative irritation reaction, nor any cutaneous sensitization.

Lyon and Sofia,

12.11.09

N. RENTERO
Ph. D. in Physiology,
Industrial and Agribusiness
Biochemistry Engineer
Responsible for the Study

M. VASSILEVA
Post-Graduate in Life and
Health Sciences
Technical and Scientific
Manager

Dr. Z. PANOVÅ, M.D.
Dermatologist Investigator

This study was conducted by INSTITUT D'EXPERTISE CLINIQUE- BULGARIE,
registered by the Bulgarian Health Authorities
Professor Rumyana YANKOVA, MD., Ph. D., Head ofthe Dermatology
and Allergology Department of Plovdiv Medical University

QUALITY CONTROL

This study was conducted in conformity with the Standard Operating Procedures of the Clinical Research Centre, the signed protocols and "in the spirit" of the general principles of the Good Clinical Practices (ICH topic E6- CPMP/ICH/135/95).

The quality control of the clinical studies is carried out periodically. It is designed to ensure that all critical phases (investigational product applications and examinations or measurements) of a particular study type are controlled, at least once quarterly, for the studies carried out during this time period. Types and dates of quality controls are given below. When the quality control of a critical phase has been conducted on another study (of the same type) than the study concerned by the present report, the sentence "on identical study" is added to the "Type of quality control".

The results of these quality controls were reported to the Investigator, to the Dermatologist and to the General Management.

Type of quality control	Dates of quality controls	Dates of reports to the Investigator and the Dermatologist	Dates of reports to the General Management
. Critical phase(s) (on identical study)	7 July 2009	8 July 2009	14 July 2009
. Raw data: Induction	15 July 2009	16 July 2009	22 July 2009
. Raw data: Challenge	3rd August 2009	4 August 2009	7 August 2009

This report has been controlled by I.E.C. Bulgarie and I.E.C. France Quality Units. It constitutes an accurate and complete reflection of the raw data generated in this study.

	Date of quality control	Date of reports to the investigator and the Dermatologist	Date of report to the General Management
Report (vs. compiled data):	29 October 2009	29 October 2009	29 October 2009

Signature: 02/11/09

Cecile AUZEAU
Quality Executive Manager

5. INVESTIGATIONAL PRODUCT

Designation	
Formula	Dicaprylyl Carbonate 30.984% Face and Body Oil
Batch n°	F1 of 18/05/2009
Physical form	oily solution
I.E.C. identification code	B090821 005711
Analytical control	The conformity of the investigational product with the labelling was guaranted by the Sponsor. In addition, information on the investigational products was provided to the investigational laboratory (colour, physical form). For this type of study, no analytical dosage was made and neither stability, nor absorption of the investigational product was evaluated by I.E.C..
Colour	yellow
Packaging	plastic flask
Quantity supplied (packaging included)	4 x 63 g
Quantity used	55 g
Date of receipt	12 June 2009
Storage	Under lock and key, protected from heat (between + 5°C and + 25° C). The unused investigational products will be destroyed at the end of the study. A sample of the investigational product was kept in the concerned facility (I.E.C. Bulgarie) for 6 months as of the date of dispatch of the final report. From this date and unless advised of the contrary by the Sponsor, the investigational product will be destroyed.
Particular precaution	In the absence of information from the Sponsor about a possible interaction with the other investigational products, no particular precaution was taken during the positioning of this product on the subjects' back.

10.2. Subjects

Number of subjects recruited	146
Number of subjects who came to I.E.C. Bulgarie	124
Number of subjects included by the Dermatologist Investigator	111
Number of subjects discontinued from the study . before the 1st reading . during the induction phase . during the rest phase - Non related adverse event - Non related serious adverse event - Related adverse event - Related serious adverse event - Concomitant treatment(s) incompatible with the study - Consent withdrawal by the subject - Lost to follow up - Emergence of a non inclusion criterion - Decision of the Dermatologist Investigator -Violation of the protocol	7 (n° 03, 20, 22, 35, 80, 107, 109) 1 (n° 80) 5 (n° 20, 22, 35, 107, 109) 1 (n° 03) / / / / / 5 (n° 20, 35, 80, 107, 109) / 2 (n° 03, 22) / /
Number of subjects for the analysis of the results . for the evaluation of Primary Cutaneous Irritation . for the evaluation of Cumulative Irritation . for the evaluation of Cutaneous Sensitisation	 108 104 104

The physical characteristics of the subjects are summarized in the following table:

Subjects	Primary Cutaneous Irritation	Cumulative Irritation	Cutaneous Sensitisation
Number	108	104	104
Females	102	98	98
Males	6	6	6
Age minimum (y.o.)	18	18	18
Age maximum (y.o.)	69	69	69

10.3. Results

The observations and clinical examinations are listed in the following appendix (Tables I to VII).

Percentage of subjects having presented with one or several well visible to severe irritation reactions (score ≥ 2), during the induction	0 %
Mean Irritation Index (M.I.I.) of the induction Classification of the investigational product	0 ✓ non-irritant: M.I.I. < 0.25 o slightly irritant: M.I.I. [0.25 - 1[o moderately irritant: M.I.I. [1 - 2[o very irritant: M.I.I. [2 - 3[o severely irritant: M.I.I. [3 – 4[
Percentage of the sensitization reactions observed	0%
Reactions considered as serious adverse events linked to the investigational product	0%

11. CONCLUSION

In conclusion and given the results obtained under the experimental conditions adopted, the single and repeated epicutaneous applications of the investigational product designated as " (Dicaprylyl Carbonate 30.984% Face and Body Oil- batch n° F1 of 18/05/2009)", under occlusive patch, in the healthy adult subject, did not provoke any primary or cumulative irritation reaction, nor any cutaneous sensitisation.

PERITESCO
Centre de Recherche Biomédicale

STUDY REPORT

VERSION 1 (21 October 2009)

OCULAR AND CUTANEOUS ACCEPTABILITY STUDY OF A BODY, FACE AND HAIR OIL DURING 4 WEEKS UNDER OPHTHALMOLOGICAL AND DERMATOLOGICAL SUPERVISION

SPONSOR	INVESTIGATOR
ADDRESSES	
[redacted]	Investigating Laboratory: PERITESCO 4, rue Villedo 75001 PARIS

STAFF IN CHARGE OF THIS STUDY	
[redacted]	Main Investigator: Dr. M. PERICOI Ophthalmologist Co-investigators : Dr. S. LAQUIEZE Dr. S. LEWY Dr.M.RAFAA Dermatologists

REFERENCES	
DT 033594 Dicaprylyl Carbonate 30.984% Face and Body Oil F2C2 du 18/May/2009	5699-43-0D1

[redacted]

Document consisting of 108 pages

PERITESCO
4, rue Villedo
75001 PARIS

0825 05 15 65
Fax: 01 53 29 97 25
R.C.S. Paris B 389 377 672

STUDY ADMINISTRATIVE STRUCTURE AND TECHNICAL STAFF

1. Investigating Laboratory

1.1. Address

PERITESCO
4, rue Villedo
75001 PARIS

1.2. Staff

Main Investigator	Dr. M. PERICOI Ophthalmologist D.E.A of Dermopharmacy Clinical Toxicology and Pharmacology Degree Clinical Expert (Decree of the 29th of June, 1985)
Co-Investigators	Dr. S. LAQUIEZE Dermatologist Expert in Phase I, II and III clinical studies in Dermatology and Cosmetology Clinical Expert (Decree of the 29th of June 1985) Dr. S. LEWY Dermatologist Dr. M.RAFAA Dermatologist
Study Manager	Mrs. A. LADURELLE
Report Writing	Mrs. V. DE MATOS Assistant
Statistical Analysis Manager	Mrs. S. ICKOVA
Technical staff in charge of the study	Miss L. LEMONNIER Miss S. GARCIA Technicians

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CERTIFICATE OF QUALITY POLICY

TITLE: OCULAR AND CUTANEOUS ACCEPTABILITY STUDY OF A BODY, FACE AND HAIR OIL DURING 4 WEEKS UNDER OPHTHALMOLOGICAL AND DERMATOLOGICAL SUPERVISION

REFERENCES: DT 033594
5699-43-0D1

INVESTIGATIONAL PRODUCT: Dicaprylyl Carbonate 30.984% Face and Body Oil F2C2 du 18/May/2009

MAIN INVESTIGATOR: Dr. M. PERICOI, Ophthalmologist.

To my knowledge, the study described in this report was carried out according to the protocol, to PERITESCO Standard Operating Procedures and respects the spirit of the standards of the Good Clinical Practice Guidelines according to the guidelines of the International Conference on Harmonization (ICH Topic E6 «Note for guidance on Good Clinical Practice CPMP/ ICH/ 135/ 95 »). the FDA (62 FR 25692 of May 9, 1997), and the EEC (Directive n° 2001120/CE of April 4, 2001).
Audits were performed in compliance with the general procedures of Quality Assurance department and in the spirit of Good Practices and of the general principles of the Good Clinical Practices according to the guidelines of the International Conference on Harmonization (ICH Topic E6 «Note for guidance on Good Clinical Practice CPMP/ ICH/ 135/ 95 »).

The following table mentions the audits that were carried out during the study, and the date of transmission of the audits reports to the investigator and the study manager:

Type of audit	Date of audit	Date of report to the investigator
Preliminary results audit	15/09/2009	15/09/2009
Report audit	19/10/2009	19/10/2009
Last in-life audit performed for the same type of study	13/1112008	05/02/2009

This report only contains the cutaneous acceptability and the cosmetic acceptability results of the investigational product. The results regarding its subjective efficacy are the aim of another report.
This report constitutes a true and faithful record of the original raw data of the investigating laboratory, generated during the performance of the study.

Miss M. HERING
Quality Policy
PERITESCO

22/10/09
date

CERTIFICATE OF QUALITY CONTROL

TITLE: OCULAR AND CUTANEOUS ACCEPTABILITY STUDY OF A BODY, FACE AND HAIR OIL DURING 4 WEEKS UNDER OPHTHALMOLOGICAL AND DERMATOLOGICAL SUPERVISION

REFERENCES: DT 033594
5699-43-0D1

INVESTIGATIONAL PRODUCT: Dicaprylyl Carbonate 30.984% Face and Body Oil F2C2 du 18/May/2009

MAIN INVESTIGATOR: Dr. M. PERICOI, Ophthalmologist.

A quality control program checked that the report presents the raw data of the study.

All the controls on the data veracity and conformity with the protocol were performed at each step of the study:

Verifications	Date	Controlled by
Protocol conformity	17/07/2009	VDM
Case report form	29/07/2009	AL
Clinical data	02/09/2009	SL
Questionnaire	14/09/2009	VDM
Preliminary results	14/09/2009	AL
Report	08/10/2009	SV

Jadurelle

Mrs. A. LADURELLE
Quality Control
PERITESCO

22/10/2009
date

METHODOLOGY

I. STUDY DESCRIPTION

1.1. Investigational product

The investigational product was supplied by [redacted]

This investigational product had the following characteristics:

Investigational product denomination and reference	Dicaprylyl Carbonate 30.984% Face and Body Oil
Batch number	F2C2 du 18/May/2009
Presentation	Yellow oil
Packaging	Pump glass flask with a metal cap
Quantity supplied	440 samples
Date of receipt	02 July 2009
Storage	Between 15°C and 25°C

All the investigational products (including the investigational products given back by the subjects at the end of the study and the possible investigational products in surplus) were destroyed within the deadline foreseen in the study protocol.

A sample of the investigational product is stored at the clinical unit where the study took place, for 6 months after sending the study report, according to the PERITESCO SOP.

1.2. Clinical methods

1.2.1. Aim of the study

This study, carried out on cosmetic products whose security was previously assessed by a toxicologist, was performed in order to confirm the safety of these products which will be used by a large amount of users under normal and reasonably foreseeable conditions of use.

The aim of the study was to confirm the ocular, peri-ocular and cutaneous acceptability of the investigational product as well as its cosmetic acceptability under normal conditions of use, as foreseen by the sponsor, under ophthalmological and dermatological control.

1.2.2. Relevancy

Cosmetic products can induce ocular, cutaneous or mucous discomfort and/or irritation signs.
The medical ophthalmologic and/or dermatological supervision of a group of subjects using a cosmetic product under normal conditions of use, the collection of functional signs and the observation of physical signs that appeared during the study period, as well as the analysis of the investigational product's imputability, enable the evaluation of the investigational product's safety, its tolerance, and the classification of its irritant potential.

The analysis of the standard deviation of each studied sign enabled the determination of the number of subjects to include in the study. The occurrence frequency standard deviations as well as physiological criteria enabled the determination of the duration of the study.

The number of subjects, the frequency of use and the duration of this study are satisfactory to study the tolerance of the investigational product.

The investigational product was applied on the face, body and hair, which corresponds to the standard use for this kind of product.

I.2.3. Study design

* Location: The study was carried out at the clinical unit of Paris.

*Design: The study was open and non-randomized.

* Timetable: - Clinical study start date: 30 July 2009
- Clinical study end date: 02 September 2009

I.2.4. Statistics

The statistical analysis was carried out in accordance with the statistical protocol included in the study protocol (See procedures in Appendix 1).

I.2.5. Subjects participating in the study

The following table gives information about the participation in the study of all the retained subjects.

	Number of subjects	Reason and day of occurrence
Recruited	52	
Non-Included	0	
Study premature withdrawals	0	
Not analyzed data	5	Subjects n°1, 7, 10, 11 and 12: Tear film break-up time measurements and colorimetric examinations were missing
Valid cases	47	

The average age of the subjects was:

Age: 50.4 ± 12.3 years old (extreme values: 21 - 73 years old).

The study was performed in three groups of subjects:
- Group 1: 20 subjects with sensitive eyes,
- Group 2: 11 subjects with non-sensitive eyes,
- Group 3: 21 subjects wearing contact lenses.

1.2.5.1. Inclusion Criteria

The voluntary subjects satisfied the following criteria:

Female,
Caucasian,
Over 18 years old,
50% of subjects presenting a normal skin,
50% of subjects presenting a dry skin,
At least 50% of subjects with a sensitive skin,
50% of subjects presenting dry hair,
50% of subjects presenting normal hair,
At least 20 subjects with sensitive eyes according to the following criteria:

- tear film break-up time inferior to 10 seconds
- and/or lid margin examination revealing a seborrheic hypersecretion with at least a slight intensity and/or a dysfunction or an atrophy of meibomius glands,
- and/or subjects fulfilling the subjective criteria of organic ocular sensitivity without optical ocular sensitivity (photophobia, astigmatism, heterophoria, cataract or corneal scars),

At least 10 subjects with non-sensitive eyes according the following criteria: who did not fulfill the sensitive eye criteria described above,
At least 20 subjects wearing contact lenses continuously (traditional soft lenses, disposable or with a month replacement or flexible)
Able and willing to give their written informed consent,
Mfiliated to the social security in accordance to the recommendations of the French Act ("Loi Huriet": n° 88.1138 - 20.12.88) about the biomedical research.

1.2.5.2. Non-inclusion Criteria

The voluntary subjects did not satisfy the following criteria:

Taking part in or planning to take part in another study during the study period
Who could not commit themselves on the absence of pregnancy or breastfeeding during the study period
Presenting a medical history of medical or psychiatric illness or major surgery, suffering from acute or chronic or progressive illnesses, or presenting a dermatological or ophthalmological pathology likely to interfere with the data of the study
Unwilling to give their written informed consent
Who could not be contacted in case of emergency by phone
PERITESCO's employees
Who did not fulfill the above inclusion criteria.

1.2.5.3. Premature study withdrawl criteria

A subject included in the study was excluded if:

The investigator judged that an adverse event was directly attributable to the investigational product,
A hypersensitive reaction or an allergic reaction directly linked to the investigational product occurred,
The subject wanted to withdraw from the study, for whatever reason, In
case the subject did not respect the study constraints,
In case of no adequacy during the study with the initially checked inclusion criteria,
Lost to follow-up subject.

1.3. Protocol amendment

No protocol amendment was requested.

1.4. Protocol deviation

The study was conducted according to the protocol specifications.
However, the following deviations were observed:

Type of de · tion Subject no	Number of subjects	Age	Type of subjects	Study duration (26<29<32 days)	Number of applications on hair (7<8<9 applications)	Number of applications on face (26<29<32 applications)	Number of applications on body (26<29<32 applications)	Missing examination
Subjects with dry hair			63.5% instead of 50%					
Subjects with normal hair			36.5% instead of 50%					
Subjects with dry skin face			23.1% instead of 50%					
Subjects with normal skin face			76.9% instead of 50%					
Subjects with dry skin body			61.5% instead of 50%					
Subjects with normal skin body			38.5% instead of 50%					
Subject no 25				34 days	11 applications	34 applications	33 applications	
Subject n°17						4 applications		
Subjects n°39, 43 45				33 days		33 applications		
Subjects n°6, 34,				33 days	10 applications	33 applications		
Subjects n°1, 7, 10 and 12								Tear film break-up time measurement and colorimetric examinations
Subject n°11							25 applications	Tear film break-up time measurement and colorimetric examinations

Type of de · tion Subject no	Number of subjects	Age	Type of subjects	Study duration (26<29<32 days)	Number of applications on hair (7<8<9 applications)	Number of applications on face (26<29<32 applications)	Number of applications on body (26<29<32 applications)	Missing examination
Subjects n°2, 9, 28 and 40					10 applications			
Subjects n°22 and 43					11 applications			
Subject n°32					12 applications			
Subject n°51					13 applications			
Subject n°8					56 applications		56 applications	

These deviations had no consequence on the validity of the observed results

II. STUDY SCHEDULE

The subjects received a daily-log where they daily recorded the use of the investigational product and the possible signs felt or observed during the use, or any other information.

ILL Initial Time

TO: before application of the investigational product

The ophthalmologist performed:
*An ocular functional signs investigation on both eyes (Groups 1, 2 and 3),
* A biomicroscopic examination of the ocular and peri-ocular structures on both eyes (Groups 1, 2 and 3),
*A colorimetric examination of the cornea and conjunctiva on the right eye (Groups 1 and 2),
* A tear film break-up time measurement on the right eye (Groups 1 and 2),
*A contact lenses examination on both eyes (Group 3).

The dermatologist performed:
*A cutaneous functional signs investigation (Groups 1, 2 and 3),
*A dermatological examination of the face, the body and the scalp with search of physical signs (Groups 1, 2 and 3).

TlO min: At least 10 minutes after application of the investigational product on face and body

The ophthalmologist performed:
*An ocular functional signs investigation on both eyes (Groups 1, 2 and 3),
* A biomicroscopic examination of the ocular and peri-ocular structures on both eyes (Groups 1, 2 and 3),
* A colorimetric examination of the cornea and conjunctiva on the right eye (Groups 1 and 2),
*A tear film break-up time measurement on the right eye (Groups 1 and 2),
—— * A...contact lenses examination on both eyes (Group 3)

Every observation was reported in the case report forms.

11.2. Final Time

The subjects arrived in the morning of the final visit, having applied the investigational product on hair, face and body the evening before, at home, in the conditions of the study.

TO: before the last investigational product application on the face

After 4 weeks of application, the subjects answered a questionnaire about the cosmetic acceptability of the investigational product (Groups 1, 2 and 3).
The dermatologist performed:
* A cutaneous functional signs investigation by analyzing the observation reported in the daily log (Groups 1, 2 and 3),
*A dermatological examination of the face, body and scalp with search of physical signs (Groups 1, 2 and 3).

T10 min: at least 10 minutes after the last investigational product application on the face

The ophthalmologist performed:
* An ocular functional signs investigation by analyzing the observations recorded in the daily log (Groups 1, 2 and 3),
* A biomicroscopic examination of the ocular and peri-ocular structures on both eyes (Groups 1, 2 and 3),
* A colorimetric examination of the cornea and conjunctiva on the right eye (Groups 1 and 2),
*A contact lenses examination on both eyes (Group 3).

Every observation was reported in the case report forms.

III. INVESTIGATIONAL PRODUCT'S APPLICATION

During the study, the investigational product was used as follows:

Application area	The face, body and hair
Applied quantity	Necessary and sufficient for this kind of product
Frequency	Face and body: once a day Hair: twice a week
Duration	4 weeks
Total number of applications for the whole panel	Face: 1531 applications Body: 1530 applications Hair:508 applications
Conditions of use	The investigational product was applied once a day on the face and the body, and twice a week on the hair, during 4 weeks. The first application was performed at the clinical unit on the face and the body. The subjects came to the clinical unit for the final visit having applied the investigational product on the hair, face and body at home, the night before. A last application was performed at the clinical unit when coming for the final visit, on the face only, so that the ophthalmological examinations could be done. Directions for use: - Application on the body in the morning in place of the body care - Application on the face in the evening in place of the night care -Application on the hair in the evening The number of times to spray on per application was left to subjects' convemence. The oil had to be sprayed directly on the hair and the body but not on the face (for the application on the face, spray the product in the hand and then apply on the face) Do not rinse. Precaution before use: In case of contact with the eyes, rinse immediately and thoroughly.
Constraints of the study	Allowed (excegt when coming to the clinical unit for the control visits): - Usual hygiene products for the face and the body (soap, foaming scrub, shower gel, ...). -Usual make-up removers, -Usual shampoos and conditioners, -Usual face care product in the morning, -Usual body care product in the evening, - Light face make-up (powder and blusher) and lip make-up with usual products. Not allowed: - Any other product of the same kind, - Any other face care product in the evening, - Any other body care product, in the morning, - Any other care product for the hair, the evenings when the investigational product was applied, - Eye make-up, - Any change of other cosmetic habits.

IV. ETHICAL AND JURIDICAL CONSIDERATIONS

IV.1. Ethics

The study, without any direct therapeutic aim, was carried out according to the most recent recommendations of the World Medical Association (Helsinki Declaration of 1964, and its successive updates). As this study is not concemed with the French Act n° 88-1138 of 20 December 1988, about the protection of subjects involved in biomedical research, and its successive updates, the most recent one being Act n° 2004-806 of 9 August 2004, the CPP authorization was not required. However, the principles of this Act were respected, with the exception of the recording of the subjects in a national file and the submission of the documents related to the study to an Independent Ethics Committee.

The investigational product did not contain and was not derived from material with specific risks as defined by the Commission decision n° 2000/418/CE, modified by the Commission decision n°200112/CE.

IV.2. Conditions to obtain the subjects' informed consents

On the inclusion day, the investigator or the person delegated by the investigator provided to the subject detailed information about the study modalities so that the subject could decide whether or not she wanted to participate in the study. The investigator or the person delegated by the investigator ensured that the subject obtained answers to any question she asked concerning her participation in the study.
Two copies of the informed consent were signed and dated by the subject and then checked, countersigned and dated by the investigator or the person delegated by the investigator.

IV.3. Insurance

The study was covered by the insurance contract subscribed by the sponsor, civil liability contract covering the studies on healthy subjects, by AIG Europe, contract n°7.109.393.

Additionally, the investigating laboratory subscribed a civil liability insurance by AGF, contract n° 41 263 662.

IV.4. Study filing

The investigating laboratory retains a copy of the signed protocol and its possible amendments, of the signed financial agreement, of every version of the reports, the original case report forms and everything that was used to fill them in, the informed consent forms, the source documents and all the documents related to the study for a period of ten years after completion of the study. The whole of the computerized data of the study will be stored on an internal network for 10 years as well.

In accordance with PERITESCO SOP, the paper documents archiving is outsourced in Societe Generale d'Archives (Archiving Site address: S.G.A, Entrepot GARONOR, E.P 405 Bat.1 Porte3, 93617 Aulnay-sous-Bois Cedex). The traceability of the documents will be the responsibility of PERITESCO, who will keep updated records of their filing address. These documents will be available for inspection within a reasonable period by an authorized sponsor representative or by the regulatory authorities.

The investigating laboratory can destroy the study archiving file only if the sponsor has given a formal signed agreement.

IV.5. Confidentiality

The investigating laboratory grants the study sponsor for data monitoring or audit, the regulation authorities, as well as the ethical committee if need be, permission to have direct access to the study source documents without violation of data confidentiality.

The confidentiality of the personal data of the subjects participating in the study was maintained throughout the study, in accordance with the Act "Informatique et liberte" of 6 January 1978, and with the Helsinki Declaration. To ensure their anonymity, a five-letter code was attributed to each subject. This code was composed of the first three letters of their surname followed by the first two letters of their first name.

The results of this study are considered as confidential information. This information, or any part of it, will not be disclosed, submitted for common publication or be the object of industrial property, unless the sponsor agreement is obtained.

The results gained through this study will remain the property of the sponsor.
Neither publication nor communication could be made without the foremost agreement of the sponsor of the study.

IV.6. Quality policy

The investigating laboratory developed a quality audit program in order to guarantee that the in-life study and the study report comply with the protocol, the Peritesco standard operating procedures are in the spirit of the standards of Good Clinical Practice Guidelines according to the International Conference on Harmonization (ICH Topic E6 «Note for guidance on Good Clinical Practice CPMP/ ICH/ 135/ 95 »), the FDA (62 FR 25692 of May 9, 1997), and the EEC (Directive no 2001120/CE of April4, 2001).

A quality policy statement mentioning the audits carried out during the study is included in this report see "Certificate of Quality Policy".

IV.7. Quality control

The protocol, the case report forms, the preliminary results and the reports are systematically submitted to quality control in order to verify that they are correctly written, complete and coherent. These controls are performed and registered throughout the study and are the object of a statement in this report.

The raw data of the study (whether on hard or electronic copy) was submitted to quality control. The date and identification of the person who performed the control of the data are also registered.

RESULTS

V. SUBJECTS' OCULAR CHARACTERISTICS

The following table presents the subjects' ocular characteristics:

Characteristics		Percentage of subjects
Ocular criteria	Sensitive eyes	38.5
	Non-sensitive eyes	21.2
	Contact lens wearers	40.4

The subjects' individual characteristics are presented in Appendix III.

VI. CLINICAL OCULAR RESULTS

VI. 1. Functional signs

No subject showed any functional sign at Initial Time TO before the first application of the product.

The following table presents the functional signs which appeared during the study in the different sub-groups.

*** Sensitive eyes panel:**

	Number of occurrences	%of subjects	Frequency %	Grade 1	Grade 2	Grade 3
Ocular stinging	0	0.00	0.00	0	0	0
Ocular burning	0	0.00	0.00	0	0	0
Foreign body feeling	0	0.00	0.00	0	0	0
Blur	0	0.00	0.00	0	0	0
Palpebral stinging or burning	0	0.00	0.00	0	0	0
Other sign	0	0.00	0.00	0	0	0

* Non-sensitive eyes panel:

	Number of occurrences	%of subjects	Frequency %	Grade 1	Grade 2	Grade 3
Ocular stinging	0	0.00	0.00	0	0	0
Ocular burning	0	0.00	0.00	0	0	0
Foreign body feeling	0	0.00	0.00	0	0	0
Blur	0	0.00	0.00	0	0	0
Palpebral stinging or burning	0	0.00	0.00	0	0	0
Other sign	0	0.00	0.00	0	0	0

* Contact lens wearers:

	Number of occurrences	%of subjects	Frequency %	Grade 1	Grade 2	Grade 3
Ocular stinging	0	0.00	0.00	0	0	0
Ocular burning	0	0.00	0.00	0	0	0
Foreign body feeling	0	0.00	0.00	0	0	0
Blur	0	0.00	0.00	0	0	0
Palpebral stinging or burning	0	0.00	0.00	0	0	0
Other sign	0	0.00	0.00	0	0	0

* Whole panel:

	Nb of occ	%of subjects	Freq. %	Average intensity	Gr 1	Gr 2	Gr 3	Delay mln	Duration mln	Irritant Freq.%	Total irritation frequency
Ocular stinging	0	0.00	0.00	0.0	0	0	0	0.00	0.00	0.00	0.00
Ocular burning	0	0.00	0.00	0.0	0	0	0	0.00	0.00	0.00	
Foreign body feeling	0	0.00	0.00	0.0	0	0	0	0.00	0.00		
Blur	0	0.00	0.00	0.0	0	0	0	0.00	0.00		
Palpebral stinging or burning	0	0.00	0.00	0.0	0	0	0	0.00	0.00		
Other sign	0	0.00	0.00	0.0	0	0	0	0.00	0.00		

Key: Nb of occ: number of occurrence
Freq.: Frequency
Gr: Grade
Occ: Occurence

The ophthalmological individual data is presented in Appendix IV.

VI.2. Physical signs

The following tables present the physical signs which appeared during the study.

		INITIAL TIME T0		INITIAL TIME T10 min					
		Average grade	Number of occurrences	Average grade	Number of occurrences	Grade 1	Grade 2	Grade 3	Bilateral occurrences
Seborrheic hypersecretion	right	0.4	20						
	left	0.4	20						
Dysfunction of meibomius glands	right	0.0	0						
	left	0.0	0						
Eyelids	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	
Bulbar conjunctival redness	right	0.0	0	0.0	0	0	0	0	0
	left	0.0	0	0.0	0	0	0	0	
Conjunctival pallor	right	0.0	0						
	left	0.0	0						
Papillae	right	0.0	0						
	left	0.0	0						
Folliculosis	right	0.0	0						
	left	0.0	0						

		FINAL TIME T10 min					
		Average grade	Number of occurrences	Grade 1	Grade 2	Grade 3	Bilateral occurrences
Seborrheic hypersecretion	droite	0.4	20	20	0	0	20
	gauche	0.4	20	20	0	0	
Lid margin	droite	0.0	0	0	0	0	0
	gauche	0.0	0	0	0	0	
Bulbar redness	droite	0.0	0	0	0	0	0
	gauche	0.0	0	0	0	0	
Conjunctival pallor	droite	0.0	0	0	0	0	0
	gauche	0.0	0	0	0	0	
Papillae	droite	0.0	0	0	0	0	0
	gauche	0.0	0	0	0	0	
Folliculosis	droite	0.0	0	0	0	0	0
	gauche	0.0	0	0	0	0	
Other sign	droite	0.0	0	0	0	0	0

The following table presents the number of subjects who showed corneal cells loss.

	Total number of corneal cells loss	Number	Surface (Grade from 0 to 10)	Depth (Grade from 0 to 3)
Initial Time TO	0			
Initial Time T10 min	0			
Final Time T10 min	0			

The following table presents the physical signs observed during the observation period.

*Initial Time TO

No	CODE	Type	Seborrheic hypersecretion (Grade)
1	BAEKA	s	1
2	JOUNI	s	1
3	MAUMA	s	1
4	PIGSY	s	1
5	ZAHSA	s	1
6	CHAEL	s	1
7	COLDE	s	1
8	HARMA	s	1
9	VAUMU	s	1
10	TREMO	s	1
11	REVMI	s	1
12	MARPA	s	1
13	BRUCA	s	1
15	GAIMA	s	1
16	BERCL	s	1
17	HATNA	s	1
18	PAVJO	s	1
19	LEVEL	s	1
20	COTPA	s	1
21	SOTSA	s	1

Key: s: Subject with sensitive eyes

*Final Time T10 min

No	CODE	Type	Seborrheic hypersecretion (Grade)
1	BAEKA	s	1
2	JOUNI	s	1
3	MAUMA	s	1
4	PIGSY	s	1
5	ZAHSA	s	1
6	CHAEL	s	1
7	COLDE	s	1
8	HARMA	s	1
9	VAUMU	s	1
10	TREMO	s	1
11	REVMI	s	1
12	MARFA	s	1
13	BRUCA	s	1
15	GAIMA	s	1
16	BERCL	s	1
17	HATNA	s	1
18	PAVJO	s	1
19	LEVEL	s	1
20	COTPA	s	1
21	SOTSA	s	1

Key: s: Subject with sensitive eyes

The ophthalmological individual data is presented in Appendix IV.

VI.3. Tear film break-up time measurements

The comparison between individual levels of break-up times before and after application was carried out using a match paired Wilcoxon test (significativity threshold= 5%).

The following table presents the results (performed in 26 subjects):

	B.U.T. values (seconds)		Statistics	
	Initial Time T0	Initial Time T10 min	Initial Time T0 / Initial Time T10 min	Difference
Sensitive eyes panel	5.47 ± 2.39	5.87 ± 2.29	p = 0.571	Not significant
Non-sensitive eyes panel	7.09 ± 2.74	6.73 ± 3.10	p = 0.672	Not significant
Whole panel	6.15 ± 2.62	6.23 ± 2.64	p = 0.934	Not significant

The ophthalmological individual data is presented in Appendix IV.

VI.4. Colorimetric examination of cornea and conjunctiva

The following tables present the staining indexes obtained at different times (performed in 26 subjects):

* **Sensitive eyes panel**

* Initial Time TO

. Surface

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate(%)	0%	0.00%	0%	0.00%
Average conjunctival rate(%)	0.00%			
Average corneal rate(%)			0.00%	

. Depth

	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0
Depth	0.00	0.00
Average depth	0.00	

* Initial Time TIO min

. Surface

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate(%)	0%	0.00%	0%	0.00%
Average conjunctival rate(%)	0.00%			
Average corneal rate(%)			0.00%	

. Depth

	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0
Depth	0.00	0.00
Average depth	0.00	

*Final Time TIO min

. Surface

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate(%)	0%	0.00%	0%	0.00%
Average conjunctival rate(%)	0.00%			
Average corneal rate(%)			0.00%	

. Depth

	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0
Depth	0.00	0.00
Average depth	0.00	

*** Non-sensitive eyes panel**

* Initial Time TO

. Surface

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate(%)	0%	0.00%	0%	0.00%
Average conjunctival rate (%)	0.00%			
Average corneal rate(%)			0.00%	

. Depth

	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0
Depth	0.00	0.00
Average depth	0.00	

*Initial Time TIO min

. Surface

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate(%)	0%	0.00%	0%	0.00%
Average conjunctival rate(%)	0.00%			
Average corneal rate(%)			0.00%	

. Depth

	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0
Depth	0.00	0.00
Average depth	0.00	

* Final Time TIO min

. Surface

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate(%)	0%	0.00%	0%	0.00%
Average conjunctival rate (%)	0.00%			
Average corneal rate(%)			0.00%	

. Depth

	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0
Depth	0.00	0.00
Average depth	0.00	

* **Whole panel**

* Initial Time TO

. Surface

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate (%)	0%	0.00%	0%	0.00%
Average conjunctival rate (%)	0.00%			
Average corneal rate(%)			0.00%	

. Depth

	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0
Depth	0.00	0.00
Average depth	0.00	

*Initial Time TIO min

. Surface

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate(%)	0%	0.00%	0%	0.00%
Average conjunctival rate(%)	0.00%			
Average corneal rate(%)			0.00%	

. Depth

	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0
Depth	0.00	0.00
Average depth	0.00	

*Final Time TlO min

. Surface

	Superior conjunctiva	Inferior conjunctiva	Superior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0	0	0
Rate (%)	0%	0.00%	0%	0.00%
Average conjunctival rate(%)	0.00%			
Average corneal rate(%)			0.00%	

. Depth

	Sur:>erior cornea	Inferior cornea
Number of subjects with a grade different from 0	0	0
Depth	0.00	0.00
Average depth	0.00	

* Results of colorimetric global indexes of the investigational product (maximal values between the difference between the colorimetric index Initial Time TlOmin and Initial Time TO and between difference between the colorimetric index Final Time TlOmin and Initial Time TO):

	Results
Maximal conjunctival index	**0.00%**
Maximal corneal index	**0.00%**

VII. SUBJECTS' CUTANEOUS CHARACTERISTICS

The following table presents the subjects' cutaneous characteristics:

Characteristics		Percentage of subjects
Skin type	Sensitive skin	50.0
	Non-sensitive skin	50.0
Face skin nature	Normal skin	76.9
	Dry skin	23.1
Body skin nature	Normal skin	38.5
	Dry skin	61.5
Hair nature	Normal hair	36.5
	Dry hair	63.5

The subjects' individual characteristics are presented in Appendix III.

VIII. CLINICAL CUTANEOUS RESULTS

VIII.1.Application the investigational product on hair

VIII.1.1. Functional signs

*Initial Time:

	Number of occurrences	%of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous stinging	0	0.0	0.00	0	0	0	0
Pruritus	1	1.9	1.00	1	0	0	0
Burning feeling	0	0.0	0.00	0	0	0	0
Discomfort feeling	0	0.0	0.00	0	0	0	0
Tugging feeling	1	1.9	1.00	1	0	0	0

* Final Time:

	Number of occurrences	%of subjects	Freq. %	Average intensity	Gr 1	Gr 2	Gr 3	Gr 4	Duration grade
Cutaneous stinging	0	0.0	0.00	0.00	0	0	0	0	0.0
Pruritus	0	0.0	0.00	0.00	0	0	0	0	0.0
Burning feeling	0	0.0	0.00	0.00	0	0	0	0	0.0
Discomfort feeling	0	0.0	0.00	0.00	0	0	0	0	
Tugging feeling	0	0.0	0.00	0.00	0	0	0	0	

Key: Freq: Frequency
Gr: Grade

The following tables present the subjects who showed functional signs before the first application of the investigational product (Initial Time TO).

No subject felt any functional signs during the observation period.

No	CODE	Nature	Pruritus (Grade)	Tugging feeling (Grade)
5	ZAHSA	S	1	1

Key: S: Subject with dry hair

The dermatological individual data is presented in Appendix V.

VIII.2. Physical signs

The following tables present the physical signs which appeared during the study.

* Initial Time TO:

	Number of occurrences	%of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4
Erythema	7	13.5	1.57	5	0	2	0
Dryness	4	7.7	1.50	3	0	1	0
Roughness	0	0.0	0.00	0	0	0	0
Desquamation	15	28.8	1.33	12	1	2	0

* Final Time:

	Number of occurrences	%of subjects	Freq. %	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4
Erythema	5	9.6		1.40	4	0	**1**	0
Dryness	**1**	1.9		2.00	0	**1**	0	0
Roughness	0	0.0		0.00	0	0	0	0
Desquamation	3	5.8		1.00	3	0	0	0

Key: Freq : Frequency

The following tables present the subjects who showed functional signs during the study.

*Initial Time.

No	Code	Nature	Erythema (Grade)	Dryness (Grade)	Desquamation (Grade)
1	BAEKA	S	0	0	1
2	JOUNI	S	0	0	1
4	PIGSY	S	3	0	0
8	HARMA	S	1	0	0
16	BERCL	S	0	0	1
17	HATNA	S	0	0	1
20	COTPA	N	0	0	1
26	PITNA	N	0	0	3
27	THISU	N	3	0	0
32	DELMA	S	1	0	1
34	CORMY	S	0	3	0
36	FAVCL	S	1	0	0
37	BAUFR	S	0	1	1
39	CORNA	N	0	1	1
41	LAUMA	S	1	0	1
43	GUIMA	S	0	0	3
44	DESGH	N	0	0	1
45	MARDE	N	0	0	2
47	BARMA	S	0	1	1
52	METNA	S	1	0	1

Key: S: Subject with dry hair
N: Subject with normal hair

* Final Time.

No	Code	Nature	Erythema (Grade)	Dryness (Grade)	Desquamation (Grade)
2	JOUNI	S	0	0	1
8	HARMA	S	1	0	0
20	COTPA	N	0	0	1
27	THISU	N	3	0	0
32	DELMA	S	1	0	0
34	CORMY	S	0	2	0
36	FAVCL	S	1	0	0
52	METNA	S	1	0	1

Key: S: Subject with dry hair
N: Subject with normal hair

The dermatological individual data is presented in Appendix V.

VIII.3.Application the investigational product on face and body

VIII.3.1. Functional signs

* Initial Time:

	Number of occurrences	%of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous stinging	0	0.0	0.00	0	0	0	0
Pruritus	0	0.0	0.00	0	0	0	0
Burning feeling	0	0.0	0.00	0	0	0	0
Discomfort feeling	0	0.0	0.00	0	0	0	0
Tugging feeling	6	11.5	2.00	1	4	1	0

* Final Time:

	Number of occurrences	%of subjects	Freq. %	Average intensity	Gr 1	Gr 2	Gr 3	Gr 4	Duration grade
Cutaneous stinging	1	1.9	0.20	1.00	1	0	0	0	3.0
Pruritus	0	0.0	0.00	0.00	0	0	0	0	0.0
Burning feeling	0	0.0	0.00	0.00	0	0	0	0	0.0
Discomfort feeling	0	0.0	0.00	0.00	0	0	0	0	
Tugging feeling	0	0.0	0.00	0.00	0	0	0	0	

Key: Freq : Frequency
Gr: Grade

The following tables present the subjects who showed functional signs during the study.

* Initial Time:

No	CODE	Type	Face nature	Body nature	Tugging feeling (Grade)
16	BERCL	n	S	S	1
24	DUPST	s	N	N	3
25	MEDOL	n	N	S	2
28	BENLI	s	N	S	2
35	PIOAN	s	S	N	2
53	TOUJE	n	S	S	2

Key: s: Subject with sensitive skin
n: Subject with non-sensitive skin
S: Subject with dry skin
N: Normal skin

* Final Time:

					Cutaneous stinging	
No	CODE	Type	Face nature	Body nature	Grade	Number
45	MARDE	s	N	N	1	1

Key: s Subject with sensitive skin
N: Subject with normal skin

The dermatological individual data is presented in Appendix V.

VIII.4. Physical signs

The following tables present the physical signs which appeared during the study.

*Initial Time TO:

	Number of occurrences	% of subjects	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4
Erythema	3	5.8	1.67	1	2	0	0
Dryness	44	84.6	2.25	12	15	11	6
Roughness	24	46.2	2.75	0	11	8	5
Desquamation	7	13.5	2.57	1	2	3	1

* Final Time:

	Number of occurrences	%of subjects	Freq. %	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4
Erythema	2	3.9		1.50	1	1	0	0
Dryness	36	69.2		2.19	9	14	10	3
Roughness	16	30.8		2.38	2	8	4	2
Desquamation	5	9.6		2.00	2	2	0	1

Key: Freq : Frequency

The following tables present the subjects who showed physical signs during the study.

* Initial Time.

No	Code	Type	Face nature	Body nature	Erythema (Grade)	Dryness (Grade)	Roughness (Grade)	Desquamation (Grade)
1	BAEKA	s	S	N	0	1	0	0
2	JOUNI	s	N	S	0	2	2	0
3	MAUMA	s	S	S	0	3	3	2
4	PIGSY	s	N	S	0	3	2	0
5	ZAHSA	n	N	S	0	3	0	0
6	CHAEL	s	N	N	0	1	0	0
7	COLDE	n	N	N	0	1	0	0
9	VAUMU	s	N	N	2	1	0	0
10	TREMO	s	N	S	0	1	0	0
11	REVMI	s	N	S	0	1	0	0
12	MARPA	s	N	N	0	1	0	0
13	BRUCA	n	N	N	0	2	2	0
17	HATNA	n	N	S	0	2	2	0
18	PAVJO	n	N	S	0	4	4	3
19	LEVEL	s	N	N	0	4	4	0
20	COTPA	n	N	S	0	1	0	0
22	PLIMI	s	N	S	1	3	0	0
23	BELNA	s	N	S	2	1	0	0
25	MEDOL	n	N	S	0	2	2	0
26	PITNA	n	N	S	0	2	2	0
27	THISU	s	S	S	0	4	4	0
28	BENLI	s	N	S	0	2	0	0
29	FERDA	n	N	S	0	2	3	0
30	JARED	n	N	N	0	1	0	0
32	DELMA	s	N	S	0	3	2	0
33	BARSO	s	S	S	0	2	0	0
34	CORMY	s	S	S	0	2	2	0
35	PIOAN	s	S	N	0	2	0	0
36	FAVCL	s	S	N	0	3	3	0
37	BAUFR	s	S	S	0	4	4	3
38	COHJE	n	S	S	0	3	3	3
39	CORNA	n	N	N	0	4	4	4
40	PRUMA	n	N	S	0	1	0	0
42	OUAKA	n	N	N	0	2	2	0
43	GUIMA	n	N	N	0	3	2	2
44	DESGH	n	N	N	0	1	0	0
45	MARDE	s	N	N	0	3	3	0
46	DEVAN	s	N	S	0	2	0	0
47	BARMA	s	N	S	0	4	3	0
48	PETMA	n	N	S	0	3	3	0
49	DECPA	s	N	S	0	2	0	1
50	DONPA	n	N	S	0	2	2	0
51	BIACE	n	N	N	0	2	0	0
53	TOUJE	n	S	S	0	3	3	0

Key: s: Subject with sensitive skin
n: Subject with non-sensitive skin
S: Subject with dry skin
N: Subject with normal skin

*Final Time.

No	Code	Type	Face nature	Body nature	Erythema (Grade)	Dryness (Grade)	Roughness (Grade)	Desquamation (Grade)
2	JOUNI	s	N	S	0	3	2	0
3	MAUMA	s	S	S	0	3	0	2
4	PIGSY	s	N	S	0	1	0	0
5	ZAHSA	n	N	S	0	2	0	0
6	CHAEL	s	N	N	0	1	0	0
7	COLDE	n	N	N	0	1	0	0
9	VAUMU	s	N	N	2	0	0	0
11	REVMI	s	N	S	0	1	0	0
13	BRUCA	n	N	N	0	2	2	0
17	HATNA	n	N	S	0	2	2	1
18	PAVJO	n	N	S	0	3	3	0
19	LEVEL	s	N	N	0	4	3	0
20	COTPA	n	N	S	0	3	3	0
22	PLIMI	s	N	S	1	3	0	0
23	BELNA	s	N	S	0	1	0	0
25	MEDOL	n	N	S	0	2	1	0
26	PITNA	n	N	S	0	2	2	0
27	THISU	s	S	S	0	2	2	0
28	BENLI	s	N	S	0	2	0	0
29	FERDA	n	N	S	0	1	2	0
30	JARED	n	N	N	0	1	0	0
32	DELMA	s	N	S	0	2	0	0
34	CORMY	s	S	S	0	2	0	0
35	PIOAN	s	S	N	0	2	0	0
36	FAVCL	s	S	N	0	3	2	0
37	BAUFR	s	S	S	0	4	4	1
38	COHJE	n	S	S	0	3	3	2
39	CORNA	n	N	N	0	4	4	4
40	PRUMA	n	N	S	0	1	0	0
42	OUAKA	n	N	N	0	1	0	0
43	GUIMA	n	N	N	0	2	0	0
45	MARDE	s	N	N	0	3	0	0
46	DEVAN	s	N	S	0	2	0	0
47	BARMA	s	N	S	0	2	1	0
48	PETMA	n	N	S	0	3	2	0
49	DECPA	s	N	S	0	2	0	0
53	TOUJE	n	S	S	0	3	0	0

Key: s: Subject with sen sitive skm
n: Subject with non-sensitive skin
S: Sub ject with dry skin
N: Sub ject with normal skin

The dermatological individual data is presented in Appendix V.

IX. COSMETIC ACCEPTABILITY OF THE INVESTIGATIONAL PRODUCT

The following tables present the percentages obtained for each item of the questionnaire. These results, also expressed in number of subjects, are calculated on the 52 subjects who took part in the whole study.

Q	AGREE	SLIGHTLY AGREE	NEITHER AGREE, NOR DISAGREE	SIGHTLY DISAGREE	DISAGREE
COSMETICITY					
The color of the product is pleasant	73.1% (38)	19.2% (10)	5.8% (3)	0.0% (O)	1.9% (1)
The texture of the product is pleasant	67.3% (35)	23.1% (12)	5.8% (3)	1.9% (1)	1.9% (1)
The aspect of the product is .Qleasant	65.4% (34)	28.8% (15)	3.8% (2)	0.0% (O)	1.9% (1)
The scent of the product is pleasant	73.1% (38)	19.2% (10)	0.0% (0)	3.8% (2)	3.8% (2)
The product is easy to apply	67.3% (35)	28.8% (15)	1.9% (1)	1.9% (1)	0.0% (0)
The application is homogeneous/uniform	63.5% (33)	25.0% (13)	5.8% (3)	3.8% (2)	1.9% (1)
ACCEPTABILITY					
The product is gentle for the skin	76.9% (40)	19.2% (10)	0.0% (0)	1.9% (1)	1.9% (1)
The product is comfortable	73.1% (38)	21.2% (11)	1.9% (1)	1.9% (1)	1.9% (1)
The product is suitable for me	55.8% (29)	25.0% (13)	15.4% (8)	1.9% (1)	1.9% (1)
The product is suitable for my skin type	50.0% (26)	30.8% (16)	9.6% (5)	7.7% (4)	1.9% (1)
APPRECIATION					
Globally, the product is pleasant	57.7% (30)	34.6% (18)	7.7% (4)	0.0% (O)	0.0% (0)

ANSWERS QUESTIONS	YES	NO
Would you like to continue using the product	80.8% (42)	19.2% (10)
At the end of the test. would you purchase the product (regardless of its price)	75.0% (39)	25.0% (13)

X. INVESTIGATIONAL PRODUCT'S WEIGHING

The investigational product was weighed before the first application and after 4 weeks of use.

The average quantity of used investigational product was:

-Average quantity of investigational product: 313.9 ± 43.7 g (extreme values: 228.0-378.0 g), i.e. 10.5 g per subject and per application.

The investigational product's weighing table is presented in Appendix VI.

XI. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

In this study, no adverse event or serious adverse event was observed by the investigator.

DISCUSSION - CONCLUSION

XII. SUBJECTS' CHARACTERISTICS

The following table presents the subjects' characteristics:

Characteristics		Percentage of subjects
Ocular criteria	Sensitive eyes	38.5
	Non-sensitive eyes	21.2
	Contact lens wearers	40.4
Skin type	Sensitive skin	50.0
	Non-sensitive skin	50.0
Face skin nature	Normal skin	76.9
	Dry skin	23.1
Body skin nature	Normal skin	38.5
	Dry skin	61.5
Hair nature	Normal hair	36.5
	Dry hair	63.5

XIII. DISCUSSION

XIII.1. Ocular acceptability of the investigational product

(a) Functional signs investigation and contact rate.

The functional signs are classified in analytical categories. This classification is made according to the opinion and the experience of the investigator, and according to the nature of the signs, their intensity, duration and their physiopathology.

The following table presents the frequency of functional signs.

Functional signs	Frequency apparition
Ocular irritation functional signs	0.00%
Mechanical ocular functional signs	0.00%
Physico-chemical ocular functional signs	0.00%
Palpebral functional signs	0.00%

The investigational product did not induce any appearance of ocular and palpebral functional signs.

The contact rate of the investigational product with the eyes is 3.85%, which is low for this kind of product.

(b) Biomicroscopic examination

The investigational product did not induce any ocular physical sign, which shows an absence of conjunctival and corneal irritant potential.

The investigational product did not induce any palpebral physical sign, which shows an absence of palpebral irritant potential.

(c) Addtional ocular examinations

(1) Tear film break-up time measurement.

This measurement was performed in 26 subjects (missing data for subjects n°1, 7, 10, 11 and 12).

The investigational product does not significantly modify the tear film stability (the B.U.T. increases from 6.15 to 6.23).

The investigational product therefore respects the ocular surface defense abilities.

(2) Colorimetric examination of cornea and conjunctiva

This examination was performed in 26 subjects (missing data for subjects n°1, 7, 10, 11 and 12).

The colorimetric examination revealed a maximal corneal index of 0.00% and a maximal conjunctival index of 0.00%, which shows an absence of toxicity to the conjunctiva and to the cornea.

(3) Contact lenses examination

The investigational product did not alter the contact lenses and did not induce any pathology specific to contact lens wearers (deposit index: 0%).

(d) Results summary

The clinical examinations revealed for the investigation product an ocular irritation rate of 0.00/2000 i.e. 0.00% and an ocular comfort rate of 500.00/500 i.e. 100.00%.

The following table presents the results:

Items		Results
Functional signs	Irritant ocular	0.00%
	Mechanical ocular	0.00%
	Physico-chemical ocular	0.00%
	Palpebral	0.00%
Physical signs	Bulbar conjunctival redness	No occurrence
	Corneal cell loss	No occurrence
B.U.T.		Initial Time TO : 6.15 secondes Initial Time T10min : 6.23 secondes Not significant modification
Staining evaluation	Maximal conjunctival index	0.00%
	Maximal corneal index	0.00%
Contact lenses deposit index		0%
Ocular irritation rate		0.00%
Ocular comfort rate		100.00%

The analysis of the impact the investigational product has on the ocular structures enables the determination of the following characteristics:

Investigational product kinetics	Low contact
Remanence on tear film	Unknown
Corneal epithelium	Non toxique
Bulbar conjunctiva	Non toxique
Conjunctival epithelium	Non toxique
Lid margin	Non toxique
Contact lenses compatibility	Very good
Functional tolerance	Very good
Investigational product chronic use	No foreseeable risk

The ocular functional and physical signs analysis enables the consideration that the investigational product shows a **practically nil ocular irritant potential,** which is very good for this kind of product.

The palpebral functional and physical signs analysis enables the consideration that the investigational product shows a **practically nil palpebral irritant potential,** which is very good for this kind of product.

(e) Investigational product comparison

The following table shows the different appearance frequencies of ocular irritation functional signs for BODY OILS compared to the investigational product's frequency under study.

FREQUENCIES OF OCULAR IRRITATION FUNCTIONAL SIGNS FOR BODY OILS			
Minimal frequency	Average frequency	Maximal frequency	**Product frequency**
0.00%	0.98%	6.46%	**0.00%**

The investigational product presents a very good functional tolerance .compared to other products of the same kind.

XIII.2. Cutaneous acceptability of the investigational product

XIII.2.1. Application the investigational product on the hair

The following table presents the **evolution** of the **signs** observed at the beginning of the study.

		% of occurrences		
	Number of occurrences	Increased	Decreased	Unchanged
Pruritus	**1**	0,0	**100.0**	0.0
Tugging feeling	**1**	0,0	**100.0**	0.0
Erythema	**7**	0,0	**28.6**	**71.4**
Dryness	**4**	0.0	**100.0**	0.0
Desquamation	**15**	0,0	**80.0**	**20.0**

Comments

(a) Safety

No significant clinical manifestation of intolerance or allergy induced any premature withdrawal from the study.

Note: Subject n°17 stopped the application of the investigational product on the face only on Day 3 because of a dryness occurrence on her face, as well as a burning feeling. Before the first application of the product, this subject presented dryness and roughness of slight intensity on the face. This subject applied the investigational product on hair and body as per the protocol study.

(1) Functional signs

The functional signs of irritation combine the following signs: cutaneous stinging, pruritus and burning feeling with an intensity and/or duration meaning an irritation.

The investigational product did not induce any functional sign of irritation.

(2) Physical signs

The investigational product did not induce any physical sign of irritation.

(3) Conclusion

Considering these observations, the investigational product presents a very good safety of use and a practically nil cutaneous irritant potential when applied on the hair in the conditions of this study.

(b) Comfort

(1) Functional signs

New signs

The investigational product did not induce any discomfort functional sign.

Evolution of the pre-existing signs

100.0% of prurit and tugging feelings present at the beginning of the study decreased during the observation period.

(2) Physical signs

New signs

The investigational product did not induce any appearance of physical sign expressing a modification of the cutaneous state during the observation period.

Evolution of the pre-existing signs

100.0% of erytherna and desquamation occurrences present at the beginning of the study decreased or remained unchanged during the observation period.

100.0% of dryness occurrences present at the beginning of the study decreased during the observation period.

(3) Conclusion

Consequently, the investigational product is considered as very comfortable when applied on the hair in the conditions of this study.

XIII.2.2. Application the investigational product on the face and the body

The following table presents the new signs which appeared during the study on the face and the body:

	Number of occurrences	%of subjects	Freq. %	Average intensity	Grade 1	Grade 2	Grade 3	Grade 4	Duration grade
Cutaneous stinging	1	1.9	0.07	1.00	1	0	0	0	3.0
Roughness	2	3.8		3.50	0	0	1	1	
Desquamation	1	1.9		1.00	1	0	0	0	

Key: Freq: frequency

The following table presents the subject who felt a functional sign (functional irritation sign):

					Cutaneous stinging	
No	CODE	Type	Face nature	Site	Grade	Number
45	MARDE	s	N	Face	1	1

Key: s: SensitiveSkin
N: Normal skin

The following table presents the subjects who felt a physical sign (physical sign expressing a modification of the cutaneous state):

No	Code	Type	Face nature	Body nature	Site	Dryness (Grade)	Roughness (Grade)	Desquamation (Grade)
17	HATNA	n	N	S	Face	2*	2*	1
20	COTPA	n	N	S	Body	3*	3	0
39	CORNA	n	N	N	Face	4*	4	4*

Key : N : normal skin
S: dry skin
n : non-sensitive skin
* : sign already present at Initial Time

The following table presents the evolution of the signs observed during the study on the face and the body:

		% of occurences		
	Nurnber of occurrences	Increased	Decreased	Unchanged
Tugging feeling	6	0.0	100.0	0.0
Erythema	3	0.0	33.3	66.7
Dryness	44	4.5	38.6	56.8
Roughness	24	0.0	70.8	29.2
Desquamation	7	0.0	71.4	28.6

Comments

(a) Safety

No significant clinical manifestation of intolerance or allergy induced any premature withdrawal from the study.

(1) Functional signs

The functional signs of irritation combine the following signs: cutaneous stinging, pruritus and burning feeling with an intensity and/or duration meaning an irritation.

The investigational product induced the appearance of an irritation functional sign (only on the face), cutaneous stinging, of very slight intensity, of duration equivalent to one hour (by intermittence during the day or not well defined)), occurring in only 1 subject (n°45), i.e 1.9%, of the panel, with an occurrence frequency of 0.07%

(2) Physical signs

The investigational product did not induce any irritation physical sign.

(3) Comments

The frequency of irritation functional signs is about 0.1%, which totally acceptable for this kind of product, with this type of subject presenting a normal and sensitive skin.
No subject presented any irritation physical sign, which is very good for this kind of product, in this type of subjects presenting a normal or dry skin on the face and the body.

(4) Conclusion

Considering these observations, the investigational product presents a very good safety of use and a very low cutaneous irritant potential when applied on the face and the body in the conditions of this study.

(b) Confort

(1) Functional signs

New signs
The investigational product did not induce any discomfort functional sign on the face and the body.

Evolution of the pre-existing signs
100.0% of tugging feeling present at the beginning of the study on the face and/or the body decreased during the observation period.

(2) Physical signs

New signs

The investigational product induced the appearance of physical signs expressmg a modification of the cutaneous state:

Roughness, of moderate intensity on the body (1 subject) and of severe intensity on the face (1 subject), occurring in 2 subjects in total (n°20 and 39), i.e 3.8% of the panel,

Desquamation, of very slight intensity on the face, occurring in only 1 subject (n°17), i.e. 1.9% of the panel

Evolution of the pre-existing signs

100.0% of erythema, roughness and desquamation occurrences present at the beginning of the study on the face and/or body decreased or remained unchanged during the observation period.

95.4% of dryness occurrences present at the beginning of the study decreased or remained unchanged during the observation period.

The dryness occurrence present at beginning of the study on the body in subjects n°2 and 20 worsened during the observation period: From slight intensity to moderate intensity in 1 subject, and from very slight intensity to moderate intensity in 1 subject.

(3) Comments

The investigational product did not induce any discomfort functional sign, whether it be on the face or on the body, which is very good for this kind of product, in this type of subjects presenting a dry or normal skin.

5.8% of subjects presented physical signs expressing a modification of the cutaneous state on the face or the body, which is acceptable for this kind of product, in this type of subjects presenting a normal or dry skin on the face or the body.

(4) Conclusion

Consequently, the investigational product is considered as **comfortable,** when applied on the face and the body in the conditions of this study.

XIII. 3. Cosmetic acceptability of the investigational product

The following table presents the percentages of satisfaction (answers with "agree" or "slightly agree") and the percentages of dissatisfaction (answer with "slightly disagree" and "disagree") obtained for each item of the questionnaire.
These results, also expressed in number of subjects, are calculated in the 52 subjects who took part in the whole study.
The sum of the percentages is not necessarily equal to 100%, because the subjects could also answer with "Neither agree nor disagree".

Key:
S: Significant

QUESTIONS	PERCENTAGE OF SATISFACTION (number of subjects)	PERCENTAGE OF DISSATISFACTION (number of subjects)	STATISTICS
COSMETICITE			
The color of the product is pleasant	92% (48)	2% (1)	**P=1.74E-13 S**
The texture of the product is pleasant	90% (47)	4% (2)	**P=4.33E-12 S**
The aspect of the product is pleasant	94% (49)	2% (1)	**P=1.32E-13 S**
The scent of the product is pleasant	92% (48)	8% (4)	**P=1.31E-10 S**
The product is easy to apply	96% (50)	2% (1)	**P=4.53E-14 S**
The application is homogeneous/uniform	88% (46)	6% (3)	**P=6.98E-11 S**
ACCEPTABILITY			
The product is gentle for the skin	96% (50)	4% (2)	**P=5.89E-13 S**
The product is comfortable	94% (49)	4% (2)	**P=1.15E-12 S**
The product is suitable for me	81% (42)	4% (2)	**P=1.13E-10 S**
The product is suitable for my skin type	81% (42)	10% (5)	**P=2.46E-08 S**
APPRECIATION			
Globally, the product is pleasant	92% (48)	0% (0)	**P=7.11E-15 S**

The investigational product obtains good percentages of satisfaction ranging between 81% and 96%.

92% of subjects agree or slightly agree on the fact that the investigational product is globally pleasant.

80.8% of subjects would like to continue using the investigational product and 75.0% of them would purchase it.

The statistical analysis shows a significant difference between the percentages of satisfaction and the percentages of dissatisfaction for the totality of items.

XIV. CONCLUSION

In the conditions of the study, the investigational product "Dicaprylyl Carbonate 30.984% Face and Body Oil" F2C2 du 18/May/2009':

- Presents a very good ocular comfort, a very good ocular safety and a very good global ocular tolerance in subjects presenting sensitive eyes, non-sensitive eyes and wearing contact lens,
- Presents a very good palpebral tolerance,
- Presents a very good compatibility with contact lenses,
- Presents a good cutaneous tolerance when applied on the face and the body in subjects presenting normal or dry skin, and a very good cutaneous tolerance when applied on the hair in subjects presenting dry and normal hair,
- Obtains a good appreciation of its cosmetic acceptability.

XV. INVESTIGATORS' STATEMENT AND SIGNATURES

The study described in this report was carried out according to the protocol, to PERITESCO SOP and to ICH Topic E6 «Note for guidance on Good Clinical Practice CPMP/ ICH/ 135/ 95 ».

I declare that this report is an accurate account of the procedures followed during the study, and constitutes a true and faithful record of my own conclusions.

22/10/09
date

Dr. M. Pericoi
Ophthalmologist
Main Investigator
PERITESCO

22. 10 2009
date

Dr. S. LAQUIEZE
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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 13, 2016

SUBJECT: Comments on the Scientific Literature Review: Safety Assessment of Dialkyl Carbonates as Used in Cosmetics (SLR posted on CIR's website March 23, 2016)

Key Issues

It would be helpful if all available information, such as the ECHA dossiers on Dimethyl Carbonate and Diethylhexyl Carbonate were included in the SLR so that the public would have the opportunity to provide comment on all of the available information.

Information from the NICNAS assessment of Dicaprylyl Carbonate (Cetiol CC; NA/861 available from http://www.nicnas.gov.au/chemical-information/new-chemical-assessments) still needs to be added to this report.

More details regarding the developmental toxicity study (inhalation exposure of mice) of Dimethyl Carbonate can be found in the OEHHA assessment at https://valleyair.org/Workshops/postings/2010/12-29-10/04%20AppB%20OEHHA%20assessment.pdf.

Additional Considerations

Introduction - Although the title of the report only included "Methyl Acetate" it should be made clear that the report also assessed the safety of Propyl Alcohol.

Cosmetic Use - The statement concerning powder exposure needs to be updated to the version that compares powder exposure to occupational exposure.

Non-cosmetic - Please delete "(included in this assessment)" as the carbonate salts are not included in the assessment on dialkyl carbonates.

Acute Toxicity, Dermal - Please either replace "cavies" with "guinea pigs" or indicate that cavie is another name for guinea pig.

Repeated Dose Toxicity, Immunotoxicity - What were the doses (or dose volumes) of Dimethyl Carbonate applied in the 28-day dermal mouse study?

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Reproductive and Developmental Toxicity - Please include the gestation days of exposure used in the developmental toxicity study in mice exposed to Dimethyl Carbonate by inhalation.

Summary - "simple carbonate salts" needs to be corrected to "dialkyl carbonates"

Table 3 - By CIR protocol at http://www.cir-safety.org/sites/default/files/Methodology_Fall%202013.pdf, face and neck products and body and hand products are considered possible powder products, but moisturizing products are not considered possible powder products. As there are Dicaprylyl Carbonate use concentrations reported for face and neck, and body and hand products, it is not clear why there is NR in the incidental inhalation - powders row. As the 2.5% concentration for Diethylhexyl Carbonate is for a moisturizer product, it is not clear why this concentration is in the incidental inhalation - powders row.