Safety Assessment of Dialkyl Carbonates as Used in Cosmetics

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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.

1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651 ◊ FAX 202.331.0088 ◊ CIRINFO@CIR-SAFETY.ORG

ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of 6 dialkyl carbonates, which function mostly as skin conditioning agents in cosmetic products. The Panel reviewed relevant data relating to the safety of these ingredients, and concluded that the dialkyl carbonates are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

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.

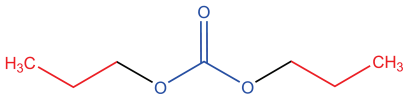
The CIR Panel has evaluated the safety of ingredients that are structurally similar to some of the ingredients that are being reviewed in this safety assessment, as well as ingredients that are components of/starting materials in the production of ingredients that are being reviewed. The Panel has issued prior conclusions for a number of specific ingredients in this review. Regarding Dipropyl Carbonate, the Panel has concluded that Propyl Alcohol is safe in the present practices of use and concentration in cosmetics.[2] Dimethy Carbonate is also being reviewed, and the Panel has concluded that Methyl Alcohol is safe as used to denature alcohol that is used in cosmetic products.[3] The alcohols may be starting materials in the production process, and, thus, a source of the alcohol as an impurity, or may be ingredient metabolites. Regarding Propylheptyl Carbonate, the Panel has concluded that Propylheptyl Caprylate is safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.[4] Safety test data on Propylheptyl Caprylate are included in this safety assessment due to the absence of available data on Propylheptyl Carbonate.

Data from chemical registration dossiers submitted to the European Chemicals Agency (ECHA) that relate to some of the ingredients that are being reviewed are included in this safety assessment. It should be noted that a chemical registration dossier may contain data on the cosmetic ingredient that is being reviewed in this safety assessment or pertinent data on a surrogate chemical. ECHA data, whether on the cosmetic ingredient or on a surrogate chemical, are included and referenced in the report text.

CHEMISTRY

Definition and General Characterization

The ingredients in this report are structurally related simple alkyl diesters of carbonic acid (definitions, Table 1[1]) . 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 diesterification product of propanol and carbonic acid (Figure 1).



Dipropyl Carbonate

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

Chemical and Physical Properties

These low-molecular-weight (< 500 g/mol) ingredients range 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),[5] with variable solubilities in water that are inversely related to alkyl chain length. Other chemical and physical properties of these ingredients are presented in Table 2.

Method of Manufacture

Dimethyl Carbonate

Most commonly, Dimethyl Carbonate is produced by transesterification of methanol and propylene carbonate.[6]

Composition/Impurities

Dicaprylyl Carbonate

A Dicaprylyl Carbonate trade name material (96.6% pure) consists of symmetric and unsymmetric carbonates (comprising C_6, C_8, and C_{10} chain lengths).[7] It was also stated that neither hazardous nor non-hazardous impurities have been detected in this trade name material. This is the material that was tested in studies that are described later in this safety assessment.

Dimethyl Carbonate

The results of a "typical analysis" of Dimethyl Carbonate were reported to be: 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).[8]

USE

Cosmetic

The safety of the Dialkyl Carbonates included in this 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).[9] 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) (Table 3). [10]

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 reportedly 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.[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.[11,12]

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 coatings, adhesives and electrolytes in lithium ion batteries.[6]

Dimethyl Carbonate

Dimethyl Carbonate is a methylating agent in organic synthesis.[14,15,16,17,18,19,20,21]

TOXICOKINETIC STUDIES

Dermal Penetration

Diethyhexyl Carbonate

The dermal absorption of 99.9% Diethylhexyl Carbonate was evaluated in an in vitro model according to Organization for Economic Co-operation and Development (OECD) Guideline 428.[22] 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 culture medium samples each were collected during a 24-h period. A validated gas chromatography with mass selective detector (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. For all 60 samples, the concentration of Diethyl Carbonate in the culture medium was < 10 μg/ml. It was concluded that Diethylhexyl Carbonate could not be detected in the receptor chamber samples for a skin exposure time of up to 24 h, and, therefore, that it is not expected to penetrate human skin. The direct measurement of Diethylhexyl Carbonate in the skin was not included in the test protocol for this study.

Absorption, Distribution, Metabolism, and Excretion

In Vitro

Diethylhexyl Carbonate

An in vitro study on Diethylhexyl Carbonate (25.77 ppm in acetonitrile) was performed using European Food Safety Authority (EFSA) Guidelines.[23] 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 Diethylhexyl Carbonate would be hydrolyzed within 4 h (hydrolysis in gastric fluid and intestinal fluid combined).

Other Carbonate Esters

A study of the porcine pancreatic elastase- (PPE-) catalyzed hydrolysis of model aliphatic and aryl carbonate (ROCOOR') esters was performed.[23]. It was noted that carbonates are esters that, when hydrolyzed, yield CO_2 and the corresponding alcohols or amines. In this study, the two aliphatic esters studied, ethyl n-butyl carbonate and ethyl cyclohexylmethyl carbonate, were hydrolyzed at lower rates (8.02×10^{-3} and 1.60×10^{-3} µmol/mg PPE/min $^{14}CO_2$) than ethyl phenyl carbonate (2.98×10^{-3} µmol/mg PPE/min), which has an effective leaving group (i.e., phenol).

Animal

Dimethyl Carbonate

Presumably, Dimethyl Carbonate is readily hydrolyzed by esterases to carbon dioxide and methanol in the environment and in the body.[24] 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 Dicaprylyl Carbonate was evaluated according to OECD Guideline 402 using groups of 10 (5 males, 5 females/group) Wistar rats.[7] 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.[25] 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).[26] 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).[20] 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.[27]

The acute dermal toxicity of Dimethyl Carbonate (concentration not stated) was evaluated using 4 rabbits. One animal died, and the LD_{50} was > 5 g/kg.[28] There was no evidence of erythema or edema.

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%).[6,29] Study details were not included.

Propylheptyl Caprylate

Groups of 5 male and 5 female Wistar rats were dosed dermally with a single semi-occlusive application of 0 or 2000 mg/kg bw Propylheptyl Caprylate, applied neat.[30] No irritation or treatment-related signs of toxicity were reported, and the dermal LD_{50} of Propylheptyl Caprylate was >2 g/kg body weight.

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).[7] 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.[31] 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).[32] 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.[20,27] 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).[29] 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%).[29] Study details were not presented.

Propylheptyl Caprylate

Six female Wistar rats were dosed orally with 2 g/kg bw Propylheptyl Caprylate in corn oil.[30] All animals had hunched posture and piloerection for 6 h after dosing, but none of the animals died during the study. The oral LD_{50} of Propylheptyl Caprylate was >2 mg/kg bw.

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).[33] The animals were exposed in a whole body inhalation chamber to Dimethyl Carbonate vapor for 4 h. The mean vapor concentration was 0.00536 g/L air minimum, and the minimum and maximum vapor concentrations were 0.00456 and 0.00577 g/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 another study, the acute inhalation toxicity of Dimethyl Carbonate was evaluated using Alderley Park specific-pathogen-free rats (2 males, 2 females).[34] The animals were placed in an exposure chamber and exposed to a nearly saturated vapor containing Dimethyl Carbonate (5000 ppm, 0.002 g/L) for 6 h. The vapor was obtained by passing air through a liquid contained in a bubbler with a sintered glass air-distributor disc. The animals were exposed to dynamic atmospheres, that is, to atmospheres that were continuously generated and passed through the exposure chamber. Control rats were also maintained in a chamber during the exposure period. After gross examination, the following organs were subjected to microscopic examination: lungs, liver, kidneys, spleen, and adrenals. Occasionally, the heart, jejunum, ileum, and thymus were examined microscopically. The following signs were observed: ocular irritation, salivation, respiratory difficulty, and incoordination. Recovery was described as rapid. Necropsy results were normal.

An acute inhalation LC_{50} of 0.14 g/L was reported for Dimethyl Carbonate after an exposure period of 4 h in a study involving rats (number and strain not stated).[20,27] 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

A concentration range-finding study was performed prior to the study that is summarized in the Immunotoxicity section.[36] Groups of 5 BALB/c mice were treated on the dorsal surface of each ear (25µl/ear) for 3 consecutive days, with acetone vehicle or increasing concentrations of Dimethyl Carbonate in acetone (up to 100%). At 2 days after the last exposure, the animals were evaluated for signs of toxicity such as loss of body weight and fatigue/lack of activity. Dermal exposure to Dimethyl Carbonate was not found to be toxic.

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.

Inhalation

Dimethyl Carbonate

The short-term inhalation toxicity of Dimethyl Carbonate was evaluated in a 3-week study using Alderley Park specific-pathogen-free rats (2 males, 2 females).[34] The animals were placed in an inhalation chamber and exposed to a Dimethyl Carbonate vapor concentration (1000 ppm, obtained by injecting a liquid into a metered stream of air by means of a controlled fluid-feed atomizer) for 6 h/day, 5 days per week (total of fifteen 6-h exposures). Control rats were also maintained in a chamber during the exposure period. The animals were exposed to dynamic atmospheres, that is, to atmospheres that were continuously generated and passed through the exposure chamber. Following gross examination, the following organs were subjected to microscopic examination: lungs, liver, kidneys, spleen, and adrenals. Occasionally, the heart, jejunum, ileum, and thymus were examined microscopically. Signs of toxicity were not observed, and necropsy results were normal.

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 groups and 1 control group) and groups of 10 Sprague-Dawley rats (5 males, 5 females/group: 2 recovery groups).[7] 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 the high-dose (1000 mg/kg/day) and control groups. 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 no-observed-effect level (NOEL) was determined to be $\geq$ 1000 mg/kg/day.

2-Ethylhexanol

Subchronic oral toxicity data on 2-ethylhexanol (hydrolysis product of Diethylhexyl Carbonate) have been proposed for use in evaluating the short-term oral toxicity of Diethylhexyl Carbonate.[37] 2-Ethylhexanol (in water) was administered orally (by gavage) for 90 days to groups of 20 B6C3F1 mice (10 males, 10 females per group) at daily doses 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. 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 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.

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] Daily doses 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 NOEL in male and female rats was 500 mg/kg/day.

Propylheptyl Caprylate

Groups of 10 male and 10 female CD/Crl:CD(SD) rats were dosed daily by gavage with 0, 100, 300, or 1000 mg/kg bw/day Propylheptyl Caprylate in soybean oil for 90 days.[30] No test-article related deaths occurred. No test-article related clinical signs of toxicity or changes in body weights or feed consumption, changes in the estrous cycle, or effects on sperm were observed, and there were no effects on any clinical chemistry or hematology parameters. A statistically significant decrease in the urinary pH values in males and females of the 300 and 1000 mg/kg bw/day groups was considered to be related to treatment. Absolute and relative liver weights were statistically significantly increased in animals of the high dose group. The change in urinary pH was attributed to the possibility of an acidic metabolite being eliminated in large doses, and the changes in liver weight were considered a non-specific adaptive change to the liver workload at the high doses, therefore, the NOAEL was established as $\geq$1000 mg/mg bw/day Propylheptyl Caprylate.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

2-Ethylhexanol

Data on the embryotoxicity/teratogenicity of 2-ethylhexanol (hydrolysis product of Diethylhexyl Carbonate) are being used to evaluate this endpoint in the absence of data on Diethylhexyl Carbonate.[39] Furthermore, in the section on Absorption, Distribution, Metabolism, and Excretion, in vitro data indicate that Diethylhexyl Carbonate is hydrolyzed in gastric fluid and in intestinal fluid. Groups of 10 pregnant female Wistar rats were dosed orally with 2-ethylhexanol (in water containing 0.005% PEG-35 castor oil) at daily doses of 130, 650, and 1300 mg/kg body weight/day on gestation days 6 through 15. 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 central nervous system 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 post-implantation 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 2-ethylhexanol for this endpoint. The NOAEL for teratogenicity was determined to be 130 mg/kg/day.

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).[24,35] 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.[24,35]

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).[7] 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).[7] 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 olyploid metaphases were observed. It was concluded that the test material was not clastogenic with or without metabolic activation in this study.

2-Ethylhexanol

Genotoxicity data on 2-ethylhexanol (hydrolysis product of Diethylhexyl Carbonate) have been proposed for evaluating this endpoint in the absence of data 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.

Propylheptyl Caprylate

The mutagenic potential of 0.31, 0.62, 1.25, 2.5, and 5.0 µl/plate Propylheptyl Caprylate was evaluated in an Ames test, with and without metabolic activation, using *Salmonella typhimurium* strains TA1535, TA1573, TA98, TA100, and TA102.[30] Dimethyl sulfoxide served as the vehicle. Propylheptyl Caprylate was not mutagenic with or without metabolic activation.

An in vitro mammalian chromosomal aberration assay was performed in Chinese hamster V79 lung fibroblasts with 22.4-2480 µg/ml Propylheptyl Caprylate.[30] The exposure time was 4 h with metabolic activation and ranged from 4-28 h without metabolic activation. Propylheptyl Caprylate was not clastogenic to Chinese hamster V79 lung fibroblasts.

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 an oral dose 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 $B_6C_3F_1$ mice.[36] In an immune phenotyping and hematology study, groups of 5 $B_6C_3F_1$ mice were exposed topically to acetone (vehicle control) 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. No effects on immune cell phenotyping (B-cells, T-cells, and T-cell subsets) were identified.

To determine whether or not exposure to Dimethyl Carbonate was immunosuppressive, the murine response to sheep red blood cells (SRBC) was examined in a study involving $B_6C_3F_1$ mice. The mice (n = 6) were exposed topically to acetone (vehicle control) 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 intraperitoneally. Statistically significant reductions in the plaque-forming cells (PFC)/spleen and specific (PFC/10^6 cells) IgM antibody against SRBC were observed after exposure to Dimethyl Carbonate. The exposure of mice to 100% Dimethyl Carbonate resulted in suppression of the values for PFC/spleen and PFC/10^6 cells (33% and 46%, respectively, versus values for vehicle-treated mice). Dimethyl Carbonate (50%) resulted in suppressions of PFC/spleen (38%) and PFC/10^6 cells (43%). Exposure to 75% Dimethyl Carbonate did not cause a statistically significant reduction in antibody production; however, the levels appeared to have been reduced when compared to those associated with the vehicle control. Cyclophosphamide caused a significant reduction in the specific spleen IgM response (78%) and total IgM response (76%), when compared to the vehicle control. There was no change in serum anti-SRBC IgM antibody levels after exposure to Dimethyl Carbonate. However, cyclophosphamide suppressed the antibody response by 66% when compared to the vehicle control. The authors concluded that Dimethyl Carbonate induced immune suppression in the murine model.

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).[7] 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 test 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 semi-occlusive 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 days 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).[26] 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.

Propylheptyl Caprylate

Propylheptyl Caprylate (applied neat; amount applied not specified) was moderately irritating to the skin of 3 female SPF albino rabbits when applied for 4 h using a semi-occlusive patch.[30]

Human

Dicaprylyl Carbonate

The skin irritation potential of a trade name material containing Dicaprylyl Carbonate was evaluated using 20 male and female volunteers.[7] 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.[45] 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; irritation was observed only on the face. At the time of the final observation, erythema was observed in 2 subjects and desquamation was observed in 5 subjects. The authors concluded that the product had very low cutaneous irritation potential when applied to the face and body.

Dimethyl Carbonate

The skin irritation potential of Dimethyl Carbonate (concentration not stated) was studied using 21 healthy adult volunteers.[46] The test material was applied (under an occlusive patch) for 48 h to the volar forearm or back of each subject. The dose per cm^2 was not stated. Skin irritation was not observed.

Propylheptyl Caprylate

Propylheptyl Caprylate was not irritating to the skin of 22 subjects when applied for 48-h using an occlusive patch.[30]

Irritation and Sensitization

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).[47] 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 over a 3-week period. The duration of exposure was 48 ± 4 h for the 1st, 2nd, 4th, 5th, 7th and 8th induction applications, and the duration of exposure was 72 ± 4 h for weekends (3rd, 6th, and 9th 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

Animal

Dicaprylyl Carbonate

The Buehler test was used to evaluate the skin sensitization potential of a trade name material containing Dicaprylyl Carbonate.[7] 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.

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 local lymph node assay (LLNA) according to OECD Guideline 429.[48] 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.[49] 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.

An LLNA was used to determine the sensitization potential of Dimethyl Carbonate.[36] Acetone served as the vehicle control. Groups of 5 BALB/c mice were exposed topically to acetone vehicle, increasing concentrations of Dimethyl Carbonate (50%, 75%, and 100%; volume = 50 µl), ora positive control [30% α-hexylcinnamaldehyde (HCA, v/v; sensitization positive control) and 0.3% 2,4-dinitrofluorobenzene (DNFB, v/v; irritancy positive control)]. Applications were made to the dorsal surface of each ear (25 µl/ear) once per day for 3 consecutive days.[36] Dimethyl Carbonate did not cause ear swelling or an increase in auricular draining lymph node proliferation, and, thus, was not found to be a sensitizer.

Propylheptyl Caprylate

In a mouse LLNA, Propylheptyl Caprylate (up to 50% in corn oil) did not induce a lymphocyte proliferative response, indicating that it is not a sensitizer.[30]

Human

Dimethyl Carbonate

The skin sensitization potential of Dimethyl Carbonate (concentration not stated) was evaluated in the maximization test using 21 adult healthy subjects (same 21 subjects tested in Skin Irritation (Human) section).[46] This study was performed after the skin irritation test. The test material was applied (under occlusion) to the same test site during 5 alternate-day 48-h periods. The dose per cm^2 was not stated. Prior to application of the test material, the test site was pre-treated for 24 h with 2.5% aqueous sodium lauryl sulfate (under occlusion). Reactions at the challenge site were scored after patch removal and 24 h later. The test material did not induce contact sensitization in this study.

OCULAR IRRITATION STUDIES

In Vitro

Dimethyl Carbonate

In an in vitro assay (rabbit corneas), Dimethyl Carbonate (solid form; no further details provided) was classified as a severe irritant.[50] 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).[7] 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.[51] 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.[52] 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).[29] At 24 h, moderate ocular irritation was reported.

Propylheptyl Caprylate

The ocular irritation potential of Propylheptyl Caprylate was evaluated in 3 female rabbits.[30] Slight conjunctival irritation was observed in all animals 1 h after instillation, and the irritation had increased to a more diffuse response in one animal at 24 h after instillation. All effects subsided within 72 h for two of the animals and by 7 days in the third animal. Propylheptyl Caprylate was considered slightly irritating to rabbit eyes.

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.[45] 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.

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).

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 in the receptor fluid after 24 h of exposure. It was determined that that Diethylhexyl Carbonate would not be expected to penetrate human skin. It should be noted that the direct measurement of Diethylhexyl Carbonate in the skin was not included in the test protocol for this study. The results of an in vitro 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), > 5 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 dermal LD_{50} in rats of Propylheptyl Caprylate was >2 g/kg body weight.

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.

The oral LD_{50} in rats was >2 g/kg for Propylheptyl Caprylate.

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. Respiratory difficulty was observed in rats exposed to Dimethyl Carbonate (0.002 g/L air) for 6 h; recovery was rapid and necropsy results were normal.

Rats were exposed to 1,000 ppm Dimethyl Carbonate in a subchronic inhalation toxicity study whereby the animals were subjected to 6-h exposures 5 days per week for 3-weeks. Signs of toxicity were not observed and necropsy results were normal.

The application of undiluted Dimethyl Carbonate to the ears of mice (25 µl/ear) for 3 consecutive days did not result in signs of toxicity. The toxicity signs evaluated included loss of body weight and fatigue/lack of activity. 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.

Data on 2-ethylhexanol have been 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 NOEL. 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.

In a subchronic oral toxicity study (90 days) on Propylheptyl Caprylate involving rats, toxic effects were not observed at doses up to 1000 mg/kg body weight/day.

2-Ethylhexanol was administered orally to rats at doses up to 1300 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 130 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.

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.

Propylheptyl Caprylate was not mutagenic in an Ames assay (≤ 5.0 µl/plate) or clastogenic in an in vitro mammalian chromosomal aberration assay (≤ 2480 µg/ml).

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 a 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.

In rabbits, Propylheptyl Caprylate was moderately irritating. In a mouse local lymph node assay, Propylheptyl Caprylate did not induce a lymphocyte proliferative response, indicating that it is not a sensitizer.

Dimethyl Carbonate (concentration not stated) was classified as a non-irritant in a 48-h occlusive patch test and as a non-sensitizer in the maximization test (occlusive patches) involving 21 adult volunteers.

The skin irritation and sensitization potential of a cosmetic investigational product (liquid) containing approximately 31% 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.

Propylheptyl Caprylate was not irritating to human skin when applied for 48 h using an occlusive patch.

In an in vitro assay (rabbit corneas), 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. 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.

Propylheptyl Caprylate was slightly irritating to rabbit eyes.

The ocular and cutaneous acceptability of a cosmetic investigational product (body, face, and hair oil) containing approximately 31% 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.

DISCUSSION

The Panel noted evidence that oral exposures to 2-ethylhexanol, a putative metabolite of Diethylhexyl Carbonate, can produce embryotoxic and teratogenic effects. The Panel further noted the in vitro toxicokinetics data demonstrating the hydrolysis of Diethylhexyl Carbonate, and agreed that toxicology data on 2-ethylhexanol (a hydrolysis product of Diethylhexyl Carbonate) support the safety assessment of Diethylhexyl Carbonate. The Panel agreed that the exposures tested are much greater than can reasonably be expected from the use of dialkyl carbonate ingredients in cosmetic products. However, the Panel noted that additional data on the dermal penetration and the rate and extent of the hydrolysis of diethylhexyl carbonate that can be expected in the skin would strengthen the safety assessment of these ingredients.

In the absence of safety test data on Propylheptyl Carbonate, the Panel agreed that data on Propylheptyl Caprylate can be used to evaluate the following toxicity endpoints for Propylheptyl Carbonate: acute dermal toxicity, acute oral toxicity, subchronic oral toxicity, genotoxicity, skin irritation, skin sensitization, and ocular irritation.

The Panel expressed concern about the irritation potential of dialkyl carbonates. Although some studies of these ingredients reported slight to well-defined irritation in animals, a study using a cosmetic investigational product containing 31% Dicaprylyl Carbonate indicated very low cutaneous irritation potential.

The issue of incidental inhalation exposure from aerosol suntan products was discussed by the Panel. They considered pertinent data indicating negative necropsy findings in rats exposed to a mean Dimethyl Carbonate vapor concentration of 5.36 mg/L air for 4 h and to 0.002 g/L air for 6 h, and, also, the results from another animal (species not stated) study indicating death due to pulmonary edema following a 2-h exposure to 8,000 ppm Dimethyl Carbonate (4-h equivalence: 20.8 mg/L). Negative short-term inhalation toxicity data on 1000 ppm Dimethyl Carbonate in a study involving rats were also considered. After reviewing these data, it was agreed that incidental inhalation exposures to Dimethyl Carbonate in aerosol suntan products would not cause adverse health effects. The Panel noted that droplets/particles from spray cosmetic products would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental

inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

Regarding the immunotoxicity study on Dimethyl Carbonate that is summarized, the Panel determined that the results are contradictory in terms of what is known about the role of the spleen in antibody production by splenic PFC and serum levels of these antibodies. The Panel agreed that these concerns should be expressed in lieu of deleting the study from the safety assessment.

CONCLUSION

The CIR Expert Panel concluded that the following 6 dialkyl carbonates are safe in the present practices of use and concentration, as described in this safety assessment, when formulated to be non-irritating.

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

*Not reported to be in current use. Were the ingredient in this group not in current use to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group.

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

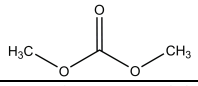
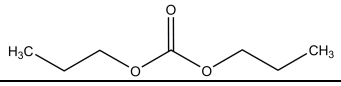
Ingredient CAS No.	Definition & Structure	Function
Dimethyl Carbonate 616-38-6	Dimethyl Carbonate is the organic compound that conforms to the formula: 	Fragrance Ingredients; Propellants; Solvents
Dipropyl Carbonate 623-96-1	Dipropyl Carbonate is the organic compound that conforms to the formula: 	Skin-Conditioning Agents - Miscellaneous

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

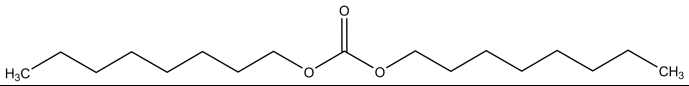
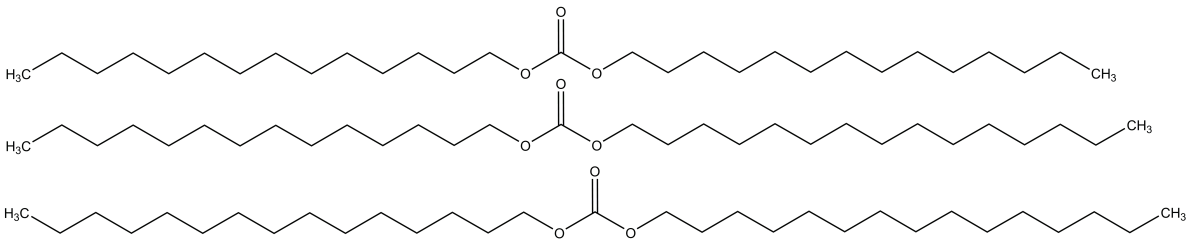
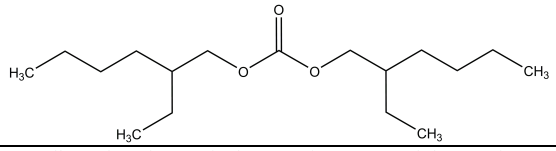
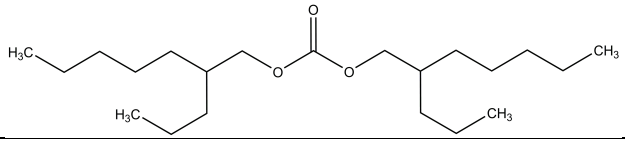
Ingredient CAS No.	Definition & Structure	Function
Dicaprylyl Carbonate 1680-31-5	Dicaprylyl Carbonate is the diester of carbonic acid and caprylyl alcohol. It conforms to the formula: 	Skin-Conditioning Agents - Emollient; Solvents
C14-15 Dialkyl Carbonate [153821-35-3 Di-C14 145197-00-8 Di-C15]	C14-15 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.[20]	Short-chain symmetrical Dialkyl Carbonates are colorless, transparent liquids with a pleasant odor.[6]
Viscosity (cP)	0.625 @ 20°C.[27]	
Molecular Mass	90.08.[6,27]	

Solubility	139 g/L in water.[6] 13.9 g/100 g.[27]	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.[6] Dimethyl Carbonate is miscible with ethanol, ethers, esters, and ketones.[27]
Melting Point (°C)	4.6.[6,27]	
Boiling Point (°C)	90.3 ˚C.[6,27]	
Density (g/cm^3)	1.069.[6] 1.07.[27]	
Reactivity		Dimethyl Carbonate has 3 reactive centers that can interact with nucleophiles: the carbonyl and 2 methyl groups.[53] 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.[8]
Octanol/Water Partition Coefficient (log Pow at °C)		0.354 at 20.[54]
	Dipropyl Carbonate	
Form	Yellow liquid.[55]	
Molecular Mass	146.19.[6]	
Solubility (g/L)	4.1 in water.[6]	
Melting Point (°C)	- 41˚.[6]	
Boiling Point (°C)	168.2.[6] 167 to 168.[55]	
	Dicaprylyl Carbonate	
Form	White liquid.[7]	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.[7]
Solubility (mg/L)	0.1 in water.[7]	
Melting Point (°C)	-22˚.[7]	
Boiling Point (°C)	330˚.[7]	
Specific Gravity (at °C)	0.8906 ± 0.00002 at 20.[7]	
Octanol/Water Partition Coefficient (log Pow at °C)	4.14 ± 0.2 at 23.5.[7]	

Table 3. Properties of Dialkyl Carbonates

Property	Value	Background Information
	C14-15 Dialkyl Carbonate	
Molecular Weight (g/mol)	474.78 – 482.83.[56]	
	Diethylhexyl Carbonate	

Form	Clear, colorless liquid.[57]
Solubility (mg/L)	< 0.03 in water.[58]
Melting Point (°C)	< -100.[57]
Boiling Point (°C)	317.[57]
Density (g/cm^3 at °C)	0.9 g/cm^3 at 20.[57]
Octanol/Water Partition Coefficient (log Pow at)	>4.1 at 21.[58]
	Bis-Propylheptyl Carbonate
Molecular Weight (g/mol)	342.56.[56]

Table 4. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[9,10]

	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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