Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics

Status: Final Report
Release Date: July 11, 2022
Panel Meeting Date: June 16-17, 2022

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Lisa A. Peterson, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., former Senior Scientific Analyst/Writer, and Regina Tucker, Scientific Analyst/Writer, CIR.

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

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 8 acryloyloxyethyl phosphorylcholine polymers as used in cosmetic products; most of these ingredients are reported to function as film formers and hair/skin conditioning agents in in cosmetics. The Panel reviewed data relevant to the safety of these ingredients in cosmetic formulations, and concluded that the acryloyloxyethyl phosphorylcholine polymers are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

The safety of the following 8 acryloyloxyethyl phosphorylcholine polymers as used in cosmetics is reviewed in this safety assessment.

Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer
C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer
Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer
Phosphorylcholine Glycol Methacrylate/PEG-10 dimethacrylate Crosspolymer
Polyphosphorylcholine Glycol Acrylate
Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer
Polyquaternium-51
Polyquaternium-61

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), most acryloyloxyethyl phosphorylcholine polymers are reported to function as film formers and hair/skin conditioning agents in cosmetic products (See Table 1).[1] Two other functions associated with ingredients in this group include humectant and viscosity increasing agent. These ingredients are all vinyl-type polymers and share in common certain phosphorylcholine acrylate monomers.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. The published data in this document were identified by conducting an exhaustive search of the world's literature. A list of the search engines and websites that are used, and the sources that are typically explored, as well as the endpoints that the Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data may be provided by the cosmetics industry, as well as by other interested parties. Please note, because little relevant data were available in the published literature, data on poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate), which is very similar structurally to Polyquaternium-51 (which is poly(2-methacryloyloxyethyl phosphorylcholine-co-n-***propyl*** methacrylate), are included in this safety assessment.

CHEMISTRY

Definition and Structure

Acryloyloxyethyl phosphorylcholine polymers have been defined as amphiphilic block copolymers comprising, at least in part, 2-acryloyloxyethyl phosphorylcholine monomers.[2] The ingredients are constructed as vinyl-type polymers and share in common these phosphorylcholine substituted acrylate monomers. For example, Polyquaternium-61 (no CAS No.) comprises the two monomers shown in Figure 1. The definitions, idealized structures (for 6 of the ingredients), and available CAS Nos. of the acryloyloxyethyl phosphorylcholine polymers included in this safety assessment are presented in Table 1.[1] The only ingredients with reported CAS Nos. in this safety assessment are Polyphosphorylcholine Glycol Acrylate (CAS No. 67881-99-6) and Polyquaternium-51 (CAS No. 125275-25-4).

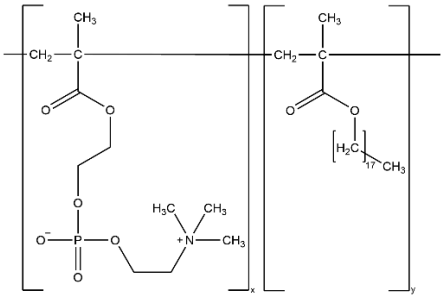


Figure 1. Polyquaternium-61

The chemical structures of Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer and Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer remain unknown. However, information provided by the International Nomenclature Committee (INC) indicate that Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer and Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer, the cellulose derived polymers (polyquaternium-10 and hydroxyethylcellulose), lack acrylate groups and are expected to copolymerize with methacryoyloxyethyl phosphorylcholine (MPC) (personal communication from the INC, November 22, 2021). Free radical reactions of polyquaternium-10 and hydroxyethylcellulose lead to the production of graft copolymers with the MPC.

Chemical Properties

Average molecular weights for acryloyloxyethyl phosphorylcholine polymers include: 338,820 Da (Polyquaternium-51), 20,182 Da (Polyquaternium-61), and 62,393 Da (Polyphosphorylcholine Glycol Acrylate).[3] These and other properties data on acryloyloxyethyl phosphorylcholine polymers are presented in Table 2.

Method of Manufacture

Ammonium persulfate is used as an initiator for the polymerization of Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer and Hydroxyethylcellulose/ Phosphorylcholine Glycol Acrylate Copolymer (personal communication from the INC, November 22, 2021).

No ingredient-specific methods of manufacture were found in the literature or submitted as unpublished data. However, some general methodologies were found in the literature, and a sample is provided below.

Amphiphilic block copolymers based on poly(2-acryloyloxyethyl phosphorylcholine) have been prepared via reversible-addition-fragmentation chain-transfer (RAFT) polymerization.[2] The block copolymers were prepared by dissolving 1 g (0.111mmol) macroRAFT agent (M_n = 9000 Da) and 2 mg (0.0121 mmol) 2,2′- azoisobutyronitrile (AIBN) in 15 ml *N*-methylpyrrolidone (NMP). 2-Acryloyloxyethyl phosphorylcholine (APC, 7.3 g [0.026 mol]) was dissolved in 25 ml methanol and added to the solution of RAFT agent and initiator in NMP. The sample was sealed and degassed by purging nitrogen through the solution, and the sample was heated in an oil bath (60 °C) with vigorous stirring. Samples were taken with a gastight syringe at preset reaction times. The conversion was determined using nuclear magnetic resonance spectroscopy (solvent: deuterated methanol/ chloroform 2:1). The polymers were purified by dissolving the final product in methanol and dialyzing for several days against water using cellulose tubular membranes (molecular weight cut-off: 10 kDa).

The synthesis of the polymer, poly(methyl methacrylate-co-methyl acrylate-co-2-acryloyloxyethyl phosphorylcholine) has also been described.[4] Radical copolymerization of methyl methacrylate (146 mg, 1.46 mmol), methyl acrylate (300 mg, 3.75 mmol), and 2-acryloyloxyethyl phosphorylcholine, initiated with α,α'-azoisobutyronitril (8 mg, 1.5 wt %) was performed in methanol (15 ml) at a concentration of 0.035 g/ml. The stirred solution was degassed with argon, the tubes were sealed, and the temperature of the solution was increased and maintained at 55 ºC. Next, the reaction was stopped by cooling at room temperature, and the tubes were stored at -18 ºC to allow precipitation of more of the polymer. The polymer was rinsed in methanol, centrifuged, and dried over phosphorus pentoxide.

Composition/Impurities

Polyphosphorylcholine Glycol Acrylate

Data on the composition of a Polyphosphorylcholine Glycol Acrylate (tradename mixture) that were received from a supplier indicate that it consists of the following: Phosphorylcholine Glycol Acrylate (40%), water (54.85%), 1,3-butylene glycol (5%), and methylparaben (0.15%).[5] Specifications for this material state 20 ppm (max) heavy metals and 2 ppm (max) arsenic.[6]

Polyquaternium-51

According to one source, the purity of Polyquaternium-51 is ≥ 94%.[7] In addition, the same source indicates that the heavy metals content of Polyquaternium-51 is ≤ 10 ppm, and the arsenic content is ≤ 2 ppm. Data on the composition of a Polyquaternium-51 (tradename mixture) that were received from a supplier indicate that it contains Polyquaternium-51 (5%) and water (95%).[5] Additionally, the specifications for Polyquaternium-51 (tradename mixture,) provided include: heavy metals (20 ppm max), /arsenic (2 ppm max), 2-methacryloyloxyethyl phosphorylcholine (100 ppm max), and butyl methacrylate (100 ppm max).[6]

Polyquaternium-61

Data on the composition of Polyquaternium-61 that were received from a supplier indicate that it consists of 100% Poyquaternium-61.[5] Additional composition data on Polyquaternium-61 (that were received include heavy metals (20 ppm max) and arsenic (2 ppm max).[6]

USE

Cosmetic

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

According to 2022 VCRP data, Polyquaternium-51 is reported to have the greatest frequency of use; it is reported to be in 317 cosmetic products, 279 of which are leave-on formulations (Table 3).[8] The results of a concentration of use survey provided by the Council in 2020 indicate that Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer has the highest reported use concentration; it is reported to be used at maximum concentrations of up to 0.18% in leave-on products (foundations).[9] Additionally, according to VCRP and Council survey data, 4 of the 8 acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment are not currently in use in cosmetic products.[8,9] These ingredients are listed in Table 4.

Cosmetic products containing acryloyloxyethyl phosphorylcholine polymers may incidentally come in contact with the eyes (e.g., 0.05% Polyquaternium-51 in eye makeup preparations) or mucous membranes (e.g., Polyquaternium-51 in bath soaps and detergents and personal cleanliness products [concentrations not reported]).

Some of these acryloyloxyethyl phosphorylcholine polymer ingredients are used in cosmetic sprays and powders that could possibly be inhaled; for example, Polyquaternium-61 is reported to be used in aerosol hair sprays at use concentrations up to 0.000006% and in face powders at up to 0.0069%. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

The acryloyloxyethyl phosphorylcholine polymers are not restricted from use in any way under the rules governing cosmetic products in the European Union.[14]

Non-Cosmetic

No non-cosmetic uses were found.

TOXICOKINETIC STUDIES

Dermal Penetration

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read across source for Polyquaternium-51)

Excised abdominal skin from male hairless rats (WBM/ILA-Ht strain) was positioned in a Franz-type diffusion cell (effective diffusion area = 3.14 cm^2).[15] A 5% fluorescent isothiocyanate-labeled poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) solution (2 ml) or free fluorescent isothiocyanate was applied on the stratum corneum. Phosphate buffered saline (~ 17 ml, receptor fluid) was on the dermal side. The skin surface was washed with distilled water at the end of the 6-h permeation experiment, and fluorescence (from the skin surface to 0 µm thickness) was observed using confocal laser scanning microscopy. At 6 h after application of 5% fluorescent isothiocyanate-labeled poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) solution, the fluorescent dye was found evenly on the skin surface. However, when free fluorescent isothiocyanate was applied, it was distributed mainly to the corneocytes (confocal laser scanning microscopy image not available).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Data on the acute toxicity of acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

Short-Term Toxicity Studies

Oral

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read across source for Polyquaternium-51)

The safety of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) of different formula weights (FW; 30,000 and 100,000 Da) was evaluated using groups (3 per group) of specific pathogen-free male Wistar rats.[16] Each copolymer was administered orally as a 10% solution in distilled water (dose volume = 10 ml/kg/d), once daily for 14 successive days. The control group was dosed with distilled water. The animals were killed 24 h after the last dose, and the following organs were removed and examined microscopically: kidneys, liver, small intestine, and large intestine. There was no evidence of lesions in these organs. Furthermore, there were no statistically significant differences in the following biomarkers of toxicity between test and control groups: serum creatinine, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase.

Subchronic and Chronic Toxicity Studies

Data on the subchronic and chronic toxicity of acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity of acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

Data on the genotoxicity of acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of acryloyloxyethyl phosphorylcholine polymers reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

ANTI-CARCINOGENICITY STUDIES

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51)

The anti-tumor activity of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) was evaluated using groups of 4 female BALB/cA nude mice.[17] Two MX-1 tumor tissue fragments (human breast tumor, 3 mm x 3 mm x 3 mm) were inoculated into the subcutaneous tissue of the bilateral dorsum of each animal. Treatment with the test substance was initiated when the tumor weight reached 200 to 300 mg. The test substance was administered i.p. (in weekly cycles) at doses of 50 mg/kg and 200 mg/kg over a 2-wk period. Relative mean tumor weight (T) of the treated group and the relative mean tumor weight of the control group (C) at any given time were determined. Antitumor efficacy was evaluated based on the lowest T/C value (%) during the experiment. Anti-tumor activity was not observed at either dose of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate). None of the animals died.

OTHER RELEVANT STUDIES

Cytotoxicity

The cytotoxicity studies below provide additional information on the toxicity potential under circumstances of direct contact of Polyquaternium-51 with cells.

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51)

The cytotoxicity of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) was evaluated in the in vitro lactase dehydrogenase (LDH) assay using the MBT-2 cell line (mouse bladder cancer cell line).[18] This assay is used to examine damage to the cell membrane, and is based on the leakage of LDH from cytosol. Cytotoxicity was not observed at test substance concentrations up to 5%.

In another cytotoxicity evaluation of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate), the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used.[17] Testing involved the following cell types (breast cancer cells): MCF-7, SK-BR-3, and MX-1 cells. The test substance (concentration not stated) did not cause growth inhibition in any of the cell types.

Inhibition of Skin Penetration

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51)

The inhibitory effect of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) on the in vitro skin permeation of methylparaben and *n*-butylparaben was evaluated.[15] Excised abdominal skin from male hairless rats (WBM/ILA-Ht strain) was positioned in a Franz-type diffusion cell (effective diffusion area = 3.14 cm^2). Methylparaben (10 mM) and n-butylparaben (1 mM) aqueous solution with or without 5% poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) were used as the donor solution. Phosphate buffered saline (receptor fluid, ~17 ml) was on the dermis side. The addition of 5% poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) decreased the skin penetration of methylparaben and *n*-butylparaben. Using the cumulative amount permeated over 8 h, the skin permeation of methylparaben and n-butylparaben was decreased by 54.8% and 85.6%, respectively, by the addition of 5% poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate). These results suggest that the inhibitory effect of 5% poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) on the skin penetration of parabens was more marked for a more lipophilic compound.

Tissue Regeneration

The toxicogenomics field aims to understand and predict toxicity using omics data in order to study systems-level responses to compound treatments. Thus, the following study, indicating an effect on gene expression by a read-across source chemical for Polyquaternium,-51, may be of some relevance in a safety evaluation.

poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51)

A study was performed to promote the understanding of initial host body reactions toward successful tissue regeneration.[19] Three-dimensional porous polyethylene scaffolds with collagen (bioactive) and poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) were used, and the genetic level of host body reactions was analyzed. Scaffolds were implanted subcutaneously (s.c.) into male Wistar rats and male C57BL/6 mice. One mouse was used for comprehensive genetic analysis and 3 rats were used for immunohistochemistry. The scaffolds were resected with surrounding tissue at 7 d after operation, and, after immunostaining of tissues for CD68 on macrophages, the early foreign body reaction to the scaffolds was assessed. Host body reactions at scaffolds were studied using a DNA microarray assay. Local ribonucleic acids (RNAs) in infiltrating cells into the porous scaffolds were extracted using a laser microdissection technique. The relationships between the expression levels of important genes for tissue regeneration on the collagen and poly(2-methacryloyloxyethyl phosphorylcholine) surface scaffold were discussed in combination with histological results. A significant number of monocytes/macrophages surrounded the scaffold. The DNA microarray assay showed that a number of genes may be involved in actively neglecting the poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate)-coated scaffold. The authors noted that these results suggest that macrophages may also play a significant role in host body suppressing reactions. The poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate)-coated scaffold slightly up-regulated genes that are related to suppression of inflammation and wound healing.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The dermal irritation and sensitization studies summarized below are presented in Table 5.

A trade name mixture containing 1.4% Polyquaternium-51 was not an irritant in the Irrectection® assay when tested at doses of 25, 50, 75, 100, and 125 µl.[20] Polyquaternim-51 was not a sensitizer in an animal study (maximization test using groups of 10 Hartley guinea pigs of a tradename mixture containing 5% aqueous Polyquaternium-51)[21] or human studies (maximization test with 25 subjects of a foundation containing 0.08125% Polyquaternium-51;[22] human repeated insult patch test (HRIPT; occlusive patches) with 212 subjects of a serum containing 0.12% Polyquaternium-51[23]). Polyquaternium-61 (25% in petrolatum) was not a sensitizer in the guinea pig adjuvant and patch test (5 Aai: (HA) outbred albino guinea pigs).[24]

OCULAR IRRITATION STUDIES

In Vitro

Polyquaternium-51

The ocular irritation potential of a trade name mixture containing 1.4% Polyquaternium-51 was evaluated in the Irrectection® assay at doses of 25, 50, 75, 100, and 125 µl.[20] The mixture was classified as a slight ocular irritant over the range of doses tested.

SUMMARY

The safety of 8 acryloyloxyethyl phosphorylcholine polymers as used in cosmetics is reviewed in this safety assessment. Most of the polymers reviewed in this safety assessment are reported to function as film formers and hair/skin conditioning agents in cosmetic products. These ingredients are all vinyl-type polymers and share in common certain phosphorylcholine acrylate monomers.

Data on the composition of a Polyphosphorylcholine Glycol Acrylate (tradename mixture) that were received from a supplier indicate that it consists of Polyphosphorylcholine Glycol Acrylate (40%), water (54.85%), 1,3-butylene glycol (5%), and methylparaben (0.15%). According to one source, the purity of Polyquaternium-51 is ≥ 94%. Data on the composition of Polyquaternium-51 (tradename mixture), received from a supplier, indicate that it contains Polyquaternium-51 (5%) and water (95%). Composition data on Polyquaternium-61 (same source) that were received indicate that it 100% Polyquaternium-61.

According to 2022 VCRP data, Polyquaternium-51 is reported to have the greatest frequency of use; it is reported to be used in 317 cosmetic products, 279 of which are leave-on formulations. The results of a concentration of use survey provided by the Council in 2020 indicate that Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer has the highest use concentration; it is reported to be used at maximum concentrations up to 0.18% in leave-on products (foundations).

A skin penetration experiment was performed using excised abdominal skin from male hairless rats (WBM/ILA-Ht strain). The test substance was a 5% fluorescent isothiocyanate-labeled poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) solution. At 6 h post-application, the fluorescent dye was found evenly on the skin surface. However, when free fluorescent isothiocyanate was applied, it was distributed mainly to the corneocytes.

The safety of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) of different FW (30,000 and 100,000 Da) was evaluated using groups (3 per group) of specific pathogen-free male Wistar rats. Each polymer was administered orally as a 10% solution in distilled water (dose volume = 10 ml/kg/d), once daily for 14 d. There was no evidence of organ lesions at microscopic examination. Additionally, there were no statistically significant differences in the following toxicity biomarkers between test and control groups: serum creatinine, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase.

In a study involving groups of 4 female BALB/cA nude mice previously injected with human breast tumor fragments, poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) was administered i.p. at doses of 50 mg/kg and 200 mg/kg) over a 2-wk period. Mortalities were not observed in either of the 2 dose groups.

The cytotoxicity of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) was evaluated in the in vitro LDH assay using the MBT-2 cell line (mouse bladder cancer cell line). Cytotoxicity was not observed at test substance concentrations up to 5%. Another assay, the MTT assay, was used to evaluate the cytotoxicity of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51; concentration not stated) in the following breast cancer cells: MCF-7, SK-BR-3, and MX-1 cells. There was no evidence of growth inhibition.

The inhibitory effect of poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) on the in vitro skin permeation of methylparaben (10 mM aqueous solution) and n-butylparaben (1 mM aqueous solution) was evaluated using excised abdominal skin (male hairless rats) in a Franz-type diffusion cell. The addition of 5% poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) decreased the skin penetration of methylparaben (by 54.8%) and n-butylparaben (by 85.6%).

A study was performed to promote the understanding of initial host body reactions toward successful tissue regeneration. Three-dimensional porous polyethylene scaffolds with collagen (bioactive) and poly(2-methacryloyloxyethyl phosphoryl-choline-co-n-butyl methacrylate) (as a read-across source for Polyquaternium-51) were implanted s.c. into 3 male Wistar rats and 1 male C57BL/6 mouse. Host body reactions at scaffolds were studied using a DNA microarray assay. This assay showed that a number of genes may be involved in actively neglecting the poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate)-coated scaffold. The poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate)-coated scaffold slightly up-regulated genes that are related to suppression of inflammation and wound healing.

A trade name mixture containing 1.4% Polyquaternium-51 was not an irritant in the Irrectection® assay when tested at doses of 25, 50, 75, 100, and 125 µl. Polyquaternim-51 was not a sensitizer in an animal study (maximization test using groups of 10 Hartley guinea pigs of a tradename mixture containing 5% aqueous Polyquaternium-51) or human studies (maximization test with 25 subjects of a foundation containing 0.08125% Polyquaternium-51; (HRIPT; occlusive patches) with 212 subjects of a serum containing 0.12% Polyquaternium-51). Polyquaternium-61 (25% in petrolatum) was not a sensitizer in the guinea pig adjuvant and patch test (5 (Aai: (HA) outbred albino guinea pigs).

The ocular irritation potential of a trade name mixture containing 1.4% Polyquaternium-51 was evaluated in the in vitro Irrectection® assay. The mixture was classified as a slight ocular irritant over the range of doses tested (25, 50, 75, 100, and 125 µl).

DISCUSSION

This assessment reviews the safety of 8 acryloyloxyethyl phosphorylcholine polymers, as used in cosmetic formulations. The Panel concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel considered the available data included in this assessment to be adequate for determining safety; data on poly (2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) were deemed appropriate for read across. Based on the molecular weights of the ingredients, significant skin penetration is not expected. The only skin penetration data in this report are on the read-across ingredient; these data demonstrate the absence of skin penetration. Furthermore, the Panel agreed that the expected absence of skin penetration essentially eliminates the need for systemic toxicity data (i.e., subchronic/chronic toxicity, carcinogenicity, and reproductive/developmental toxicity data) on the acryloyloxyethyl phosphorylcholine polymers. Furthermore, the absence of structural alerts for genotoxicity in the polymers reviewed mitigates the need for genotoxicity data.

Chemical characterization data provide an indication of residual monomer content. Because the method of manufacture of amphiphilic block copolymers based on poly(2-acryloyloxyethyl phosphorylcholine) involves purification (dialysis and rinsing) of the final product, the Panel agrees that residual monomer content is not a major concern. Additionally, the volatility of acrylate and methacrylate monomers was considered, and supports the lack of concern over monomer content.

The Panel also discussed irritation and sensitization. Concern for the skin irritation and sensitization potential of these polymers was mitigated based on the negative irritation and sensitization data for Polyquaternium-51 and Polyquaternium-61, and the absence of skin penetration by these polymers.

The chemical structures for Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer and Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer were not found in the published literature, nor were these structures provided by the cosmetics industry. However, information relating to their chemistry was provided by the International Nomenclature Committee. After reviewing the information provided, the Panel agreed that the description of the polymerization process is a plausible basis for including Hydroxyethylcellulose/Phosphoryl-choline Glycol Acrylate Copolymer and Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer in this safety assessment.

The Panel expressed concern regarding heavy metals that may be present in these ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

Finally, the Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., Polyquaternium-61 is reported to be used in aerosol hair sprays at concentrations up to 0.000006%, and in face powders at concentrations up to 0.0069%). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 8 acryloyloxyethyl phosphorylcholine polymers are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer
C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer*
Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer*
Phosphorylcholine Glycol Methacrylate/PEG-10 dimethacrylate Crosspolymer*
Polyphosphorylcholine Glycol Acrylate
Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer*
Polyquaternium-51
Polyquaternium-61

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

TABLES

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

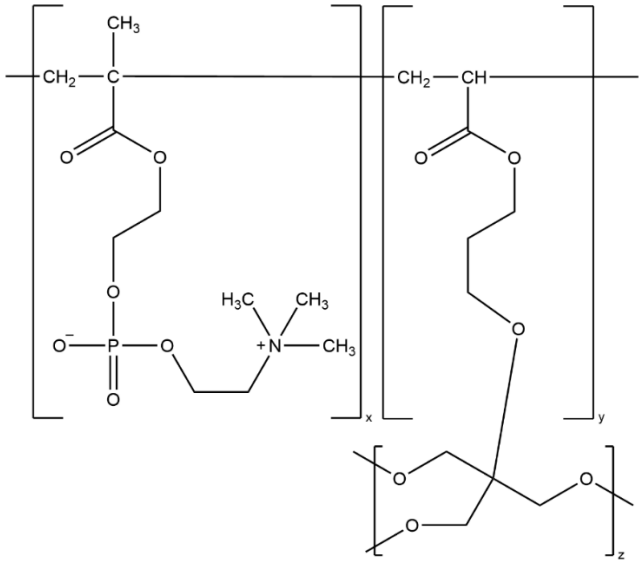
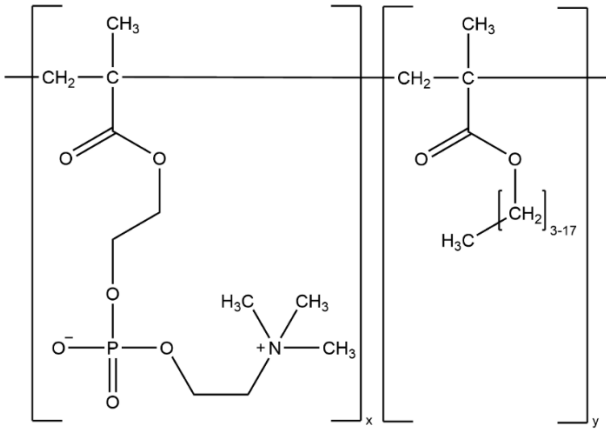
Ingredient/CAS No.	Definition & Structures	Function(s)
Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer	Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer is a copolymer formed from acrylic acid and phosphorylcholine glycol methacrylate, crosslinked with an allyl ether of pentaerythritol. 	viscosity increasing agents – aqueous.[1]
C4-18 Alkyl Methacrylate/ Methacryloyloxyethyl Phosphorylcholine Copolymer	C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer is a copolymer of methacryloyloxyethyl phosphorylcholine and C4-18 alkyl methacrylate. 	humectants
Hydroxyethylcellulose/ Phosphorylcholine Glycol Acrylate Copolymer	Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer is the copolymer formed from hydroxyethylcellulose and phosphorylcholine glycol methacrylate. *Not enough information is available about connectivity to provide a structure.*	film formers; hair conditioning agents; humectants; skin-conditioning agents - miscellaneous

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

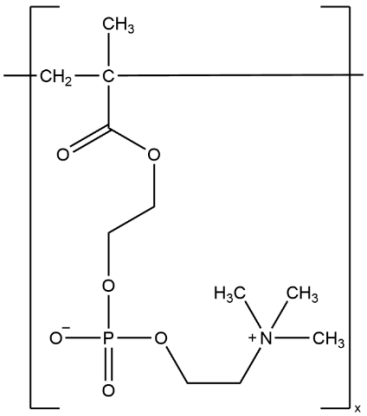
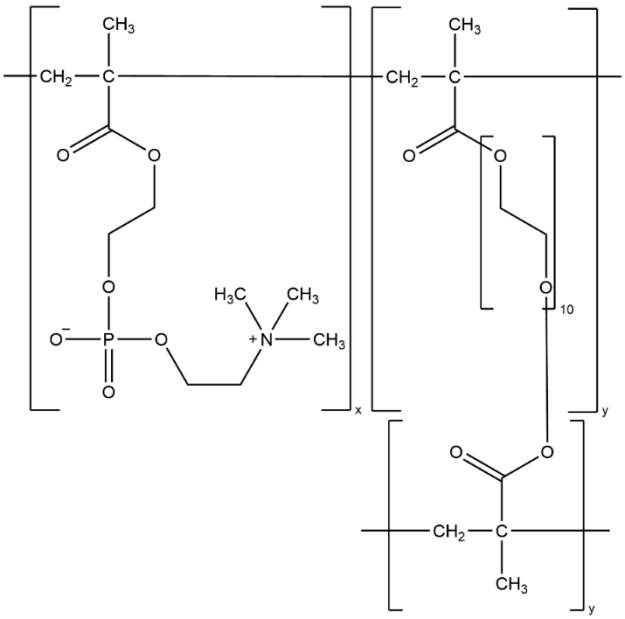
Ingredient/CAS No.	Definition & Structures	Function(s)
Polyphosphorylcholine Glycol Acrylate 67881-99-6	Polyphosphorylcholine Glycol Acrylate is the polymer that conforms generally to the formula: 	film formers; skin-conditioning agents - miscellaneous
Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer	Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer is the crosslinked polymer formed from phosphorylcholine glycol methacrylate and PEG-10 dimethacrylate monomers. 	film formers; skin-conditioning agents – humectant
Polyquaternium-10/ Phosphorylcholine Glycol Acrylate Copolymer	Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer is a copolymer of polyquaternium-10 and phosphorylcholine glycol methacrylate. *Polyquaternium-10 is a polymeric quaternary ammonium salt of hydroxyethyl cellulose reacted with 2,3-epoxypropyltrimonium chloride. Not enough information is available about connectivity to provide a structure.*	film formers; hair conditioning agents; humectants; skin-conditioning agents – emollient

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

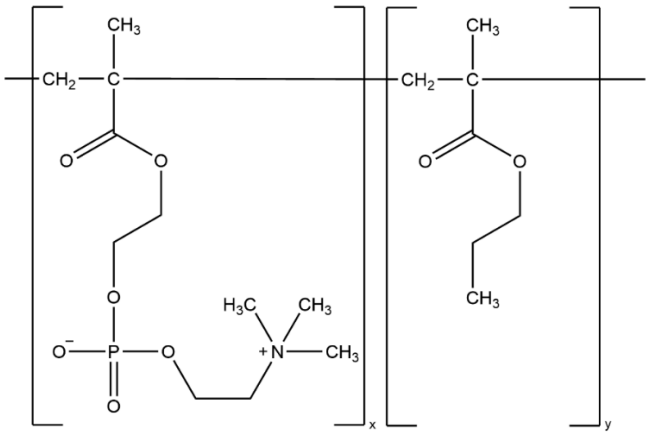
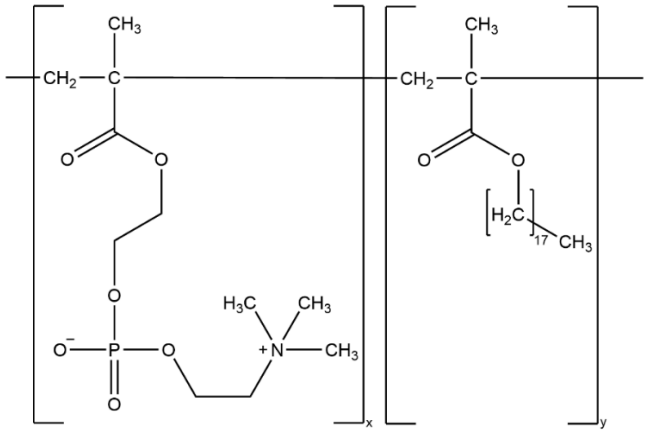
Ingredient/CAS No.	Definition & Structures	Function(s)
Polyquaternium-51 125275-25-4	Polyquaternium-51 is the polymeric quaternary ammonium salt that conforms generally to the formula: 	Film Formers; Skin-Conditioning Agents - Humectant
Polyquaternium-61	Polyquaternium-61 is the polymeric quaternary ammonium salt that conforms generally to the formula: 	Film Formers; Skin-Conditioning Agents - Humectant

Table 2. Chemical properties

Property	Value/Results	Reference
Polyquaternium-51 (tradename mixture)		
Form	Transparent liquid	6
M_w (3 different lots)	329,666; 338,513; 338,820	3
M_n (3 different lots)	87,071; 83,179; 86,294	3
M_w/M_n (3 different lots)	3.79; 4.07; 3.93	3
Viscosity (cSt, @ 40ºC)	6 - 60	6
Residue on drying (%)	4 - 6	6
Polyquaternium-61		
Form	White or pale yellow powder	6
M_w (3 different lots)	20,027; 20,182; 19,951	3
M_n (3 different lots)	8028; 8298; 7981	3
M_w/M_n (3 different lots)	2.50; 2.43; 2.50	3
Loss on drying (% max)	5; 1.8	6
Polyphosphorylcholine Glycol Acrylate (tradename mixture)		
Form	Transparent liquid	6
M_w (3 different lots)	61,179; 61,665; 62,393	3
M_n (3 different lots)	40,313; 40,671; 40,762	3
M_w/M_n (3 different lots)	1.52; 1.52; 1.53	3
Viscosity (cSt, 20ºC)	500 - 3000	6
Residue on drying (%)	43 - 48	6

Table 3. Frequency (2022) and concentration of use (2020) according to duration and type of exposure.[8,9]

	Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer		Phosphorylcholine Glycol Acrylate		Polyquaternium-51	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals*	**NR**	**0.13-0.18**	**9**	**0.0005-0.075**	**317**	**0.000005-0.14**
Duration of Use						
Leave-On	*NR*	*0.13-0.18*	*8*	*0.0005-0.075*	*279*	*0.002-0.14*
Rinse off	*NR*	*NR*	*1*	*NR*	*38*	*0.000005-0.025*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	24	0.021-0.05
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation - Sprays	NR	NR	6[a];2[b]	0.0005[b]	1;97[a];95[b]	0.01[a]
Incidental Inhalation - Powders	NR	NR	2[b]	0.0005[b]	4;95[b]	0.008-0.14[c]
Dermal Contact	NR	0.13-0.18	4	0.0005-0.075	310	0.000005-0.14
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	5	NR	7	0.0005-0.025
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	0.1
Mucous Membrane	NR	NR	NR	NR	7	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Polyquaternium-61	
	# of Uses	Conc. (%)
Totals/Conc. Range	**3**	**0.000006-0.01**
Duration of Use		
Leave-On	*2*	*0.000006-0.0069*
Rinse off	*1*	*0.01*
Diluted for (bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	NR	0.005
Incidental Ingestion	NR	NR
Incidental Inhalation - Sprays	1[a];1[b]	0.000006
Incidental Inhalation - Powders	1[b]	0.0069
Dermal Contact	2	0.001-0.0069
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	0.000006-0.01
Hair-Coloring	1	NR
Nail	NR	NR
Mucous Membrane	NR	NR
Baby Products	NR	NR

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays
[b]Not specified that these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories
[c]It is possible that these products may be powders, but it is not specified whether the reported uses are powders

Table 4. Acryloyloxyethyl phosphorylcholine polymers with no reported uses.[8,9]

C4-18 Alkyl Methacrylate/Methacryloyloxyethyl Phosphorylcholine Copolymer
Hydroxyethylcellulose/Phosphorylcholine Glycol Acrylate Copolymer
Phosphorylcholine Glycol Methacrylate/PEG-10 Dimethacrylate Crosspolymer
Polyquaternium-10/Phosphorylcholine Glycol Acrylate Copolymer

Table 5. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			IN VITRO STUDIES		
Tradename mixture containing 1.4% Polyquaternium-51	25, 50, 75, 100, and 125 µl		Skin irritation evaluated in Irrectection® assay. In vitro system involves use of proprietary solution comprised of both proteins and macromolecules in well covered by membrane. Doses applied to membrane diffused into well; proteins and macromolecules undergo conformational changes based on irritancy of diffused material. Conformational changes cause solution to become turbid, and there is direct correlation between irritancy level of material and solution's turbidity. Irritancy measured quantitatively using a spectrophotometer. Samples were left at room temperature for 24 h prior to spectrophotometry.	Mixture classified as a non-irritant over the range of doses tested	[20]
			ANIMAL		
Polyquaternium-51 (tradename mixture; 5% aqueous)	Challenge: 6.25 v/v %, 12.5 v/v %, 25 v/v%, 50 v/v%, and 100 v/v% [For preparation of test solutions, 5% aq. Poly-quaternium-51was defined as 100 v/v% original solution. Thus, the highest test concentration was 100 v/v% solution.]	Hartley guinea pigs test group: 10 animals negative control (water) and positive control (1-choloro-2,4-dinitrobenzene [DCNB])groups: 5 animals each	Sensitization potential evaluated in maximization test. For intradermal induction (on day 1), the test group was injected in the cranial part of scapular region with Polyquaternium-51, Freund's complete adjuvant(FCA) and the test material (1:1), an d FCA and water (1:1). On day 8, the skin was pretreated with an open application of 10 w/w% sodium lauryl sulfate (SLS), and on day 9, an occlusive patch containing 0.2 ml of Polyquaternium-51 was applied for 48 h. On day 22 (challenge phase), occlusive patches containing 0.1 ml of the challenge solutions were applied for 24 h. Challenge sites were evaluated at 24 nd 48 h after patch removal.	No skin reactions (erythema or edema) observed at any observation time during study. Polyquaternium-51 exhibited no skin sensitization potency.	[21]
Polyquaternium-61	25% in petrolatum	5 albino guinea pigs (Aai: (HA) outbred)/group	Skin sensitization potential evaluated in guinea pig adjuvant and patch test. A negative control group (petrolatum; only applied during challenge phase) and a positive control (DNCB) group were included. Prior to induction phase of sensitization test, topical screens were run using 4 guinea pigs (2 males, 2 females), to determine highest non-irritating concentration for topical application (under open patch conditions). On the same day, test sites treated with decreasing concentrations of test substance (suspended or dissolved in petrolatum). Test substance (0.1 ml) applied for 24 h. Reactions scored at 24 h and 48 h post-application. During first induction, each test animal received intradermal injections (2 cm x 4 cm section of shoulder area) of adjuvant/water emulsion (0.1 ml), followed by 3 topical 24-h applications (occlusive patches, in 25 mm chamber) of test substance (0.5 ml) on 3 consecutive days (1 application/day). Second week of induction involved pretreatment of patch application sites with SLS. Test substance (0.4 ml) applied topically (occlusive patches, in 25 mm chamber) for 48 h to induction site of each test animal. Challenge phase initiated 2 wk after topical induction applications. Challenge applications of Polyquaternium-61 (24 h, 0.1 ml) made to new site on flank (open patch, 5 cm x 5 cm area) of test animals. Negative control (petrolatum) was also applied to the flank (5 cm x 5 cm area) of each animal in negative control group. 1,2- DNCB (up to 1%) similarly applied to 5 positive control	Polyquaternium-61 was not a sensitizer in guinea pigs. DNCB induced sensitization.	[24]

Table 5. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			animals. Observations relating to erythema, edema, recorded at 24 h and 48 h after challenge applications.		
			HUMAN		
Foundation containing 0.08125% Polyquaternium-51.	tested neat	25 subjects (13 women, 12 men)	Skin sensitization evaluated in maximization test. During induction, 48-h occlusive patch (15 mm cotton disc) applications of the undiluted foundation (0.1 ml) were made to upper outer arm, volar forearm, or back. Induction site pretreated with 0.25% SLS (0.1 ml; under occlusive patch) for 24 h prior to test substance application. When induction patch placed over weekend, it remained in place for 72 h. SLS patch plus induction patch application sequence repeated for total of 5 induction exposures. After 10-d non-treatment period, challenge phase initiated. Single 48-h occlusive challenge patch application of the test material (0.1 ml) made to new site on opposite arm, forearm, or side of back. Challenge site pretreated for 1 h with SLS (5% aqueous). Reactions scored at 1 h post-removal and 24 h later.	No adverse or unexpected reactions observed during induction, and there no instances of contact allergy during challenge phase. The test formulation did not possess contact-sensitizing potential and not likely to cause contact sensitivity reactions under normal use conditions	[22]
Serum containing 0.12% Polyquaternium-51	tested neat	212 male and female subjects	Skin sensitization evaluated in human repeated insult patch test. Undiluted product applied, under an occlusive patch, to upper back (between scapulae and waist, lateral to midline). Induction applications made 3 x/wk for total of 9 exposures. Reactions scored at 48 h after Monday and Wednesday applications, and 24 h after Sunday removals. After 2-wk non-treatment period, challenge patch applied to original site on back and to new site. Reactions evaluated at time of patch removal and at 72 h and 96 h.	Product did not demonstrate potential for eliciting dermal irritation or sensitization	[23]

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