Safety Assessment of Alkonium Clays as Used in Cosmetics

Status:	Final Report
Release Date:	April 26, 2016
Panel Meeting Date:	March 31- April 1, 2016

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ABSTRACT

This is a safety assessment of 8 alkonium clays, including stearalkonium bentonite, as used in cosmetics. These ingredients are reported to function as dispersing agents-nonsurfactant, emulsion stabilizers, and viscosity increasing agents-nonaqueous. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the relevant data related to these ingredients. Information on other alkonium clay-derived ingredients, including quaternium-18 bentonite and benzyl-dimethyl hydrogenated tallow ammonium montmorillonite clay, were used for inference purposes. The Panel concluded that these alkonium clays are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

INTRODUCTION

This is a review of the available scientific literature and unpublished data relevant to assessing the safety of alkonium clays as used in cosmetics. These ingredients are the products of the reactions of an ammonium salt with a smectite clay. The 8 alkonium clay ingredients in this report are:

- benzalkonium montmorillonite
- benzalkonium sepiolite
- hydrogenated tallowalkonium bentonite
- quaternium-18/benzalkonium bentonite
- quaternium-90 bentonite
- quaternium-90 montmorillonite
- quaternium-90 sepiolite
- stearalkonium bentonite

In cosmetics, these ingredients are reported to function as dispersing agents-nonsurfactant, emulsion stabilizers, and viscosity increasing agents-nonaqueous according to the *International Cosmetic Ingredient Dictionary and Handbook* (Table 1).[1]

Alkonium clays are derived from a group of phyllosilicate, layered, clay-based minerals known as smectites, the most prominent of which are montmorillonite, beidellite, nontronite, saponite, bentonite, and hectorite. These alkonium clays are grouped together because of the similarities in physical structures and natures, chemical composition, exchangeable ion type, comparably small crystal size, and similarity of crystal natures of these minerals.

Other alkonium clay-derived ingredients, in particular quaternium-18 bentonite, have been reviewed by the CIR Panel and the information in these reports is useful for the determination of safety of the alkonium clays in this safety assessment. Summary data of quaternium-18 hectorite and the other previously reviewed ingredients are presented in Table 2. Ammonium hectorites (disteardimonium hectorite, dihydrogenated tallow benzylmonium hectorite, stearalkonium hectorite, and quaternium-18 hectorite), hectorite, quaternium-18 bentonite, hectorite, bentonite, montmorillonite and other clays and earths were found to be safe as used.[2-6]

Some of the components of the alkonium clays included in this safety assessment have been reviewed by the Panel and that data were useful in the determination of safety (Table 2). Quaternium-18 and stearalkonium chloride were determined to be safe as used, and benzalkonium chloride is safe up to 0.1% (upper limit of human irritation and sensitization assays).[7-9] Quaternium-90 has not been reviewed by the Panel. However, quaternium-90 and quaternium-18 are structurally similar (both are dialkyl dimonium chlorides, which vary only in fatty alkyl chain lengths, from palm oil and tallow, respectively); thus, information on quaternium-18 is likely relevant for inferring the safety of ingredients containing quaternium-90 and is included in this report.

Additionally, since quaternium-18 bentonite is useful for inference purposes in assessing the safety of the alkonium clays, data that have become available since the time of the quaternium-18 bentonite safety assessment are included in this safety assessment in the appropriate sections.

Descriptive data on the smectite clays (e.g., montmorillonite, bentonite, and sepiolite) that are useful in understanding the composition of the alkonium clays in this safety assessment are included.

Data on benzyl-dimethyl hydrogenated tallow ammonium montmorillonite clay were discovered on the European Chemicals Agency (ECHA) website.[10] While this is not the ingredient benzalkonium montmorillonite, the data for this clay is included because the similarity in chemical structures makes this information useful for inferring the safety of the ingredients in this safety assessment.

CHEMISTRY

Definition and Structure

Alkonium clays are the products of the reactions of an alkyl ammonium salt with smectite clay. Definitions of these ingredients are presented in Table 1.

Alkonium clays are derived from a group of phyllosilicate, layered, clay-based minerals, the general term for which is smectites, and the most prominent of which are montmorillonite, beidellite, nontronite, saponite, bentonite, and hectorite.[5] These clays are differentiated by variations in chemical composition involving substitutions of aluminum for silicon in tetrahedral cation sites and for aluminum, iron, magnesium, and lithium in octahedral cation sites (Figure 1).

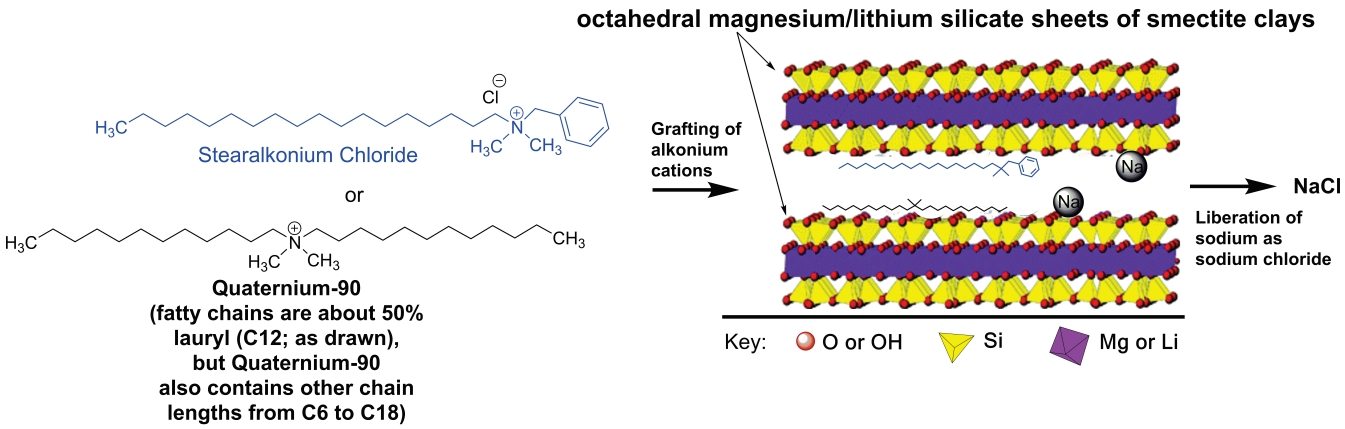

Figure 1. Synthesis of alkonium clays.

The smectite minerals are a subset of clays that include alkonium clays, and have a variable net negative charge that is balanced by sodium, calcium, or magnesium ions adsorbed externally on interlamellar surfaces.[5,11] The structure, chemical composition, exchangeable ion type, and small crystal size of smectite minerals are responsible for several unique properties, including a large chemically active surface area, a high cation exchange capacity, interlamellar surfaces having unusual hydration characteristics, and the ability to strongly modify the flow behavior of liquids. Because of isomorphous substitution of cations in the octahedral sheet during hectorite formation, the surfaces of these minerals have a delocalized net negative charge in the lattice. Cations located between 2 consecutive layers (octahedral sheets) compensate for the structural charge and keep the layers bound. Thus, cations such as sodium are attracted to the mineral surface to counterbalance the interlayer charge. These cations can be exchanged, because they are only retained in the mineral structure by electrostatic attractions.

The structures of alkonium clays depend on the charges of the layers and the lengths of the alkyl chains. Short-chain alkylammonium ions produce clays that are monolayered; clays containing long-chain alkylammonium ions are bilayered.[12,13] Smectites are highly charged and the alkyl moieties are composed of 3 kinked alkyl chains.[14] The basal spacing of alkylammonium smectites increases, in steps, with the alkyl-chain length.[15]

NATURAL SMECTITE CLAYS (BENTONITE, MONTMORILLONITE, AND SEPIOLITE)

Natural smectite clays (a.k.a. organoclays) are closely related, and the names have been used interchangeably to describe structurally similar clay minerals in the literature.[16] Natural deposits in which one of these clay minerals predominate are more commonly referred to by the predominant clay mineral's name. Thus, considering the similarity in the clay minerals of this category, the defining differentiation between the groups is the cation that is exchanged into the clay.

Bentonite is a widely distributed natural material consisting predominantly of the clay mineral montmorillonite, a smectite mineral.[11,16] Bentonite is formed of highly colloidal and plastic clays, and is produced by in-situ devitrification of volcanic ash.[17]

Montmorillonite occurs abundantly as dust at and near surface deposits of bentonite and is dispersed widely by air and moving water.[17] Montmorillonite is thus ubiquitous in low concentrations worldwide in soil, in the sediment load of natural waters, and in airborne dust. In geology, the term "montmorillonite" is ambiguous, and is used to refer to both a group of related clay minerals (where smectite is a more appropriate term) and to a specific member (montmorillonite) of that group.[18]

In structure, sepiolite can be considered transitional because it is structurally between the chain-structured and layer-structured silicates.[19,20] Sepiolite consists essentially of hydrated magnesium silicates with minor amounts of substituting elements.[21]

Sepiolite is found in sedimentary strata in arid and semi-arid climates around the world.[21] Deposits of sepiolite have been reported in China, France, Japan, Madagascar, Korea, Spain, Turkey, Tanzania, and the United States.[19,22,23]

Physical and Chemical Properties

With the exception of particle size information, chemical and physical properties were only discovered for stearalkonium bentonite (Table 3).

While the particle sizes represented below reflect the bulk size of these cation-exchanged clay materials, if the cation were to be leachable it would of course be significantly smaller than these particles. However, data from one submission on these ingredients indicate that there is no appreciable leaching of this type.[24]

Stearalkonium bentonite particle sizes were reported to be: <100 µm, approximately 90%; < 10 µm, 30%; and < 0.5 µm, 0.02%.[25] The particle size ranges of hydrogenated tallowalkonium bentonite, benzalkonium montmorillonite,

quaternium-90 montmorillonite, benzalkonium sepiolite, and quaternium-90 sepiolite are reported to be 90%-100% <100 μm, 20%-58% <10 μm, and none <0.1 μm.[26,27]

The sepiolite used to manufacture the ingredients in this safety assessment is reported to have a fiber length of 1-2 μm.[27]

The median particle size of quaternium-18 bentonite was reported to be 28 μm.[28]

In cosmetics, the ratios for cations used and clay for alkonium clays varies, depending on the type of cation and the type of clay.[28] The typical range for the cation is 20%-40% and the range for the clay is 60%-80%.

NATURAL SMECTITE CLAYS (BENTONITE, MONTMORILLONITE, AND SEPIOLITE)

Alkonium clays have a high capacity for expansion and swelling and can be easily hydrated and dehydrated.[29]

Intracrystalline adsorption is limited in sepiolite due to the sizes of the channels in the crystal structure and the non-expanding nature of the clays.[30] Therefore, only small and highly polar molecules interact with the "inner" surfaces, and nonpolar organic molecules adsorb to external surfaces. Polar organic molecules can penetrate into the channels, but preliminary outgassing of the material is usually necessary to remove "zeolitic" water. For example, short-chain alcohols can penetrate into the channels after outgassing.

Bentonite has the ability to form thixotropic gels with water and absorb large quantities of water. It also has a high cation exchange capacity.[11] The absorption of water causes an accompanying increase in volume of as much as 12-15 times its dry bulk, which helps to confer the high cation exchange capacity. Freshly exposed bentonite is white to pale green or blue and darkens in time to yellow, red, or brown.[17]

Montmorillonite clay is composed of minute particles that, under electron microscopy, appear as aggregates of irregular or hexagonal flakes or, less commonly, thin laths.[31] Differences in substitution affect, and in some cases control, morphology.

Method of Manufacture

Alkonium clays are synthesized by grafting cationic surfactants to clay (i.e., exchanging the interlayer sodium cations with a cationic surfactant). These cationic surfactants are quaternary ammonium compounds with the template formula $[(CH_3)_3NR]^+$, $[(CH_3)_2NRR']^+$, and $[CH_3NRR'R'']^+$, where R, R', and R'' are alkyl or arylalkyl hydrocarbons. For instance, in stearalkonium bentonite some of the inorganic cations of bentonite have been replaced by $[(CH_3)_2NRR']^+$, where R and R' are an octadecyl alkyl chain (i.e., stearyl group) and a benzyl group, respectively. The exchange is typically performed by the addition of the appropriate alkonium chloride (e.g., stearalkonium chloride) to an alcohol/water slurry of the clay.[32] The major by-products are inorganic chlorides (e.g., sodium chloride), which are removed during processing. This cation exchange shifts the nature of these minerals from hydrophilic to lipophilic.[32]

Impurities

As noted above, alkonium clays have a high cation exchange capacity.[11] Depending on the composition of a given cosmetic formulation, the degree to which these alkonium salts may be exchanged out of these ingredients will vary. Accordingly, there may be some resultant free alkonium salts.

Three alkonium bentonite clays with varying amounts of dimethyl dihydrogenated tallow quaternary ammonium chloride were dispersed in water at a level of 5% for 24 h.[24] When analyzed by high-performance liquid chromatography (HPLC), there was 10-20 ppm quaternary ammonium chloride present in the water phase (detection limit approximately 0.5 ppm); the saturation limit of dimethyl dihydrogenated tallow quaternary ammonium chloride is approximately 1500-2000 ppm.

Quaternium-90 bentonite was reported to have crystalline silica as an impurity at <3%.[28]

Stearalkonium bentonite may contain up to 5% quartz and up to 0.005% benzyl alcohol.[25] Benzalkonium sepiolite and quaternium-90 sepiolite were reported to be >95% pure with <0.5% silica/quartz.[27]

NATURAL SMECTITE CLAYS BACKGROUND (MONTMORILLONITE, BENTONITE, AND SEPIOLITE)

Clays contain trace elements, including antimony, arsenic, cadmium, cobalt, copper, lead, mercury, nickel, selenium, tellurium, thallium, and zinc in concentrations that are widely variable, depending on their geological origin.[33] These trace elements may be in the clay mineral structure or adsorbed on clay particles, which plays the most important role in controlling the distribution and abundance of these elements within these clays. Chemical elements in crystalline positions are usually locked in the clay, whereas those adsorbed may be mobilized and transferred to leaching solutions.

Natural bentonite may contain feldspar, cristobalite, and crystalline quartz.[34]

In an analysis of natural sepiolite samples from Japan, Spain, China, and Turkey, only the sample from China had small amounts of talc and calcite.[35]

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated on the basis of the expected use in cosmetics. The Panel utilizes data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry

in determining safety. The data received from the FDA are collected from manufacturers on the use of individual ingredients in cosmetics, by cosmetic product category, through the FDA Voluntary Cosmetic Registration Program (VCRP), and the data from the cosmetic industry are submitted in response to a survey of the maximum reported use concentrations, by category, conducted by the Personal Care Products Council (Council).

According to 2016 VCRP data, stearalkonium bentonite had the most reported uses at 388, including 385 leave-on uses and 3 rinse-off uses (Table 4).[36] The majority of these uses, 300, were in nail products, but this ingredient was also used in lipstick (63 uses) and in products used around the eye (7 uses). The only other ingredient with reported uses in the VCRP was quaternium-90 bentonite, which was reported to be used in 64 leave-on products, including 31 products used around the eye and 16 lipsticks.

In the 2015 survey conducted by the Council of the maximum use concentrations of ingredients in this group, stearalkonium bentonite was reported to be used at the highest maximum concentration at up to 6.5% in nail polish and enamel, 2.4% in lipstick, and 2.5% in eye shadow.[37-39] The ingredient with the next highest maximum concentration of use was quaternium-90 bentonite, which was reported to be used up to 6.1% in mascara and 6.1% in lipstick. It was confirmed by the Council that there were no reported uses of quaternium-90 bentonite in face powders; the face and neck product that was reported to be possibly a powder has been confirmed to be a lotion.

For 2 ingredients, no uses were reported to the VCRP, but use concentrations were provided in the industry survey. The VCRP did not report any uses for quaternium-90 montmorillonite, but the industry survey indicated that it is used in 2 types of leave-on formulations (foundations and aerosol suntan products) at concentrations up to 0.8%. No uses were reported by the VCRP for quaternium-90 sepiolite. However, the Council reported that it was used in 2 types of leave-on products (foundations and aerosol suntan products) at concentrations up to 3.2%. It should be presumed that both of these ingredients are used in at least 2 cosmetic formulations. It was reported that quaternium-90 montmorillonite and quaternium-90 sepiolite are sold together in a trade name mixture that is used in an aerosol suntan product.[40]

There were no reported uses in the VCRP or in the Council surveys for:

- hydrogenated tallowalkonium bentonite
- quaternium-18/benzalkonium bentonite
- benzalkonium montmorillonite
- benzalkonium sepiolite

Quaternium-90 montmorillonite is used in aerosol suntan products at concentrations up to 0.8% and quaternium-90 sepiolite is used in aerosol suntan products up to 3.2%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[41-44] 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.[41,44]

None of the alkonium clays named in this report are restricted from use in any way under the rules governing cosmetic products in the European Union.[45]

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) of Australia concluded that stearalkonium bentonite did not pose an unreasonable risk to public health when used in cosmetic products at concentrations up to 5%; this was reported as the expected maximum concentration of use specified by the notifying companies.[25]

Non-Cosmetic

Large volumes of smectite clay minerals are used as a binder in foundry sand; a filter/clarifier/decolorizer; pet waste/odor absorbent; oil/grease absorbent; and pesticide carrier.[46] Smaller volumes are used in medical and pharmaceutical applications, building products, radioactive waste disposal, lubricants, detergents, seed coating, and water purification.

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Data on toxicokinetics of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided.

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

Dermal – Non-Human

STEARALKONIUM BENTONITE

The dermal LD_{50} of stearalkonium bentonite was >2000 mg/kg (in deionized water) in Sprague-Dawley rats (n=5/sex).[25] The test was conducted in accordance with the Organization for Economic Cooperation and Development Test Guideline (OECD TG) 402.

Oral – Non-Human

STEARALKONIUM BENTONITE

The oral LD_{50} of stearalkonium bentonite was >5000 mg/kg (in corn oil) in albino Wistar rats (n=5/sex).[25] Clinical signs included matted fur and unkempt appearance on days 1 and 2 of observation. One male animal showed slight depression on day 4 prior to its death on day 5. At necropsy, a slightly reddened gastric mucosa was noted in a single rat. The test was conducted in a manner similar to the OECD TG 401.

BENZYL-DIMETHYL-HYDROGENATED TALLOW AMMONIUM MONTMORILLONITE CLAY

The reported oral LD_{50} for benzyl-dimethyl-hydrogenated tallow ammonium montmorillonite clay was >5000 mg/kg in Sprague-Dawley rats (n not specified).[10]

Inhalation – Non-Human

Data on the acute inhalation toxicity of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided. However, data on similar ingredients were found and are included.

QUATERNIUM-18 BENTONITE

In an acute inhalation study of quaternium-18 bentonite (average concentration 5.7 mg/L; particle size ≥10 µm, 30% ≤10 µm) in Sprague-Dawley rats (n=5/sex), the rats were exposed for 4 h 22 min in a glass chamber and were observed post exposure for 14 days.[47] There were no mortalities and no irreversible signs of toxicity observed.

BENZYL-DIMETHYL-HYDROGENATED TALLOW AMMONIUM MONTMORILLONITE CLAY

The reported inhalation LC_{50} for benzyl-dimethyl-hydrogenated tallow ammonium montmorillonite clay was >206 mg/L when Sprague-Dawley rats (n not specified) were exposed for 1 h.[10] Particle size was not specified.

Repeated Dose Toxicity

Dermal

Data on the repeated dose dermal toxicity of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided.

Oral – Non-Human

STEARALKONIUM BENTONITE

In a 28-day oral toxicity test of stearalkonium bentonite (100, 316, and 1000 mg/kg in 0.1% aqueous solution of Na-carboxymethylcellulose) in Fischer CDF(F344)/CRLBR, SPF rats (n=5/sex), the no-observed-effect-level (NOEL) was 1000 mg/kg/d when administered by gavage, based on the absence of test substance-related toxicological effects at any of the doses administered.[25] The test was conducted according to OECD TG 407. Clinical signs were similar in the treatment and control groups. Chromodakryorrhoea was observed occasionally in both the control and treatment groups. There were no differences in feed consumption or body weight gain in males. Decreased body weights were recorded for females in the high dose recovery group (duration of recovery period not specified), but were considered by the study authors to be of no toxicological relevance. No differences were observed in hematology or clinical biochemistry parameters, appearance of spontaneous lesions, or organ weight changes in the males, and no dose-related trends observed at necropsy or by histopathology examination. Decreases in organ weights in the females (heart and brain) at the end of recovery period were considered to be of no toxicological relevance, because there were no corresponding differences observed at the end of the exposure period.

Inhalation

Data on the repeated dose inhalation toxicity of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Data on reproductive and developmental toxicity of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided.

GENOTOXICITY

In Vitro

STEARALKONIUM BENTONITE

Stearalkonium bentonite (3.16, 10, 31.6, 100, and 316 µg/plate, with and without metabolic activation, in dimethyl sulfoxide) was not genotoxic to *Salmonella typhimurium* (strains TA98, TA100, TA102, TA1535, and TA1537).[25] The positive control yielded the expected results. Pronounced cytotoxicity was noted in all test strains at 316 µg/plate, with and without metabolic activation. In the assays without metabolic activation, cytotoxicity was also noted in several strains at 31.6 and/or 100 µg/plate. The test was performed in accordance with OECD TG 471.

QUATERNIUM-18 BENTONITE

An Ames assay was conducted on quaternium-18 bentonite (10, 30, 100, 300, 3000 µg/plate) in *S. typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538) with and without metabolic activation.[48] There were no signs of genotoxicity at any concentration with and without metabolic activation.

In Vivo

STEARALKONIUM BENTONITE

In a micronucleus assay, conducted in accordance with OECD TG 474, stearalkonium bentonite (1000, 1500, and 2000 mg/kg in 0.1% aqueous solution of Na-carboxymethylcellulose) was not clastogenic in Crl:NMRI BR mice (n=5/sex) when administered by gavage.[25] There were no mortalities prior to scheduled killing. The ratios between the polychromatic and normochromatic erythrocytes in the female mice at all doses were similar to that of the control data. However, the ratios were greater in males at all doses at 24 h. Because the values were within the historical negative control data ranges, the differences were not considered to be attributable to the test substance. The number of micronucleated polychromatic erythrocytes in the high dose groups (both sexes) was higher than that of the corresponding negative control group 48 h after administration. However, all counts were within the range of historical negative control data, thus the study authors considered the effect to be unrelated to the treatment. The concurrent negative and positive controls produced the expected results.

CARCINOGENICITY

Data on carcinogenicity of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

STEARALKONIUM BENTONITE

Stearalkonium bentonite (100%) was not irritating to the intact or abraded skin of New Zealand White rabbits (n=6) when administered under occlusion for 24 h.[25] The test was conducted in accordance with OECD TG 404 and the test sites were examined at 24 and 72 h after patch removal. The mean erythema/eschar and edema scores for the intact sites were 0 out of 4; the mean erythema/eschar score for the abraded sites was 0.3, and the edema score was 0.25.

The maximum non-irritating concentration for stearalkonium bentonite injected intradermally was 1.25% in distilled water when tested in albino Hartley guinea pigs (n not specified).[25] The maximum non-irritating concentration when administered topically to the skin was 60% in distilled water. No further details were provided.

Dermal - Human

QUATERNIUM-90 BENTONITE

In a 48-h patch test (n=21) of a mascara containing quaternium-90 bentonite (5.924%), it was concluded that the mascara was appropriate for consumer use.[49] No further information was provided.

Ocular-In Vivo – Non-Human

STEARALKONIUM BENTONITE

Stearalkonium bentonite (100%; 0.1 g) was severely irritating when instilled into the conjunctival sac of New Zealand White rabbits (n=7).[25] The test was conducted in accordance with OECD TG 405 and the rabbits were observed for 7 days after exposure. If the test substance was still present in the eye at 24 h after exposure, the eye was rinsed with distilled water. The most severe outcome observed for conjunctiva/redness was grade 3 (diffuse beefy red) in all rabbits 24 h after instilling the test substance. By day 7, only 1 rabbit exhibited a grade 2 response (more diffuse, crimson red, individual vessels not easily discernible). A grade 4 response for conjunctiva/chemosis (swelling with lids about half-closed to completely closed) was observed in 5 of 6 rabbits examined 24 h post exposure. One rabbit in this group exhibited a grade 2 response (obvious swelling with partial eversion of the lids) on day 7. The highest score for conjunctiva/discharge of grade 3 (discharge with moistening of the lids and hairs and of a considerable area around eye) was observed in 2 of 6 rabbits at 24 h post exposure. This was resolved by day 7. Corneal opacity of grade 2 (easily discernible translucent areas, details of iris slightly obscured) was observed in 2 of 6 rabbits at 24 h post exposure. A highest score of grade 3 (opalescent areas, no details of iris visible, size of pupil barely discernible) was observed in 1 of 6 animals at 48 h post exposure. One rabbit still exhibited a grade 4 for opaqueness; the iris was invisible on day 7. Five of 6 rabbits exhibited a grade 1 iridial inflammation response (sluggish reaction) with the effect persisting in 1 rabbit through day 7.

Stearalkonium bentonite (31-36 mg in 0.1 mL; vehicle not specified) was slightly irritating to the conjunctiva of female New Zealand White rabbits (n =3).[25] Neither cornea nor irises were affected. Slight conjunctival redness was observed in 2 rabbits from 1 through 48 h after exposure. Slight-to-moderate chemosis of the conjunctiva was observed in 2

rabbits at 1 through 48 h after exposure. Ocular discharge was noted in 2 rabbits from 1 to 24 h after administration. The test was conducted in accordance with OECD TG 405.

Ocular-In Vivo – Human

QUATERNIUM-90 BENTONITE

A 4-week use study (n=53; group 1: 21 with sensitive eyes, group 2: 11 with non-sensitive eyes, group 3: 21 wore contact lenses) of an eyeliner that contained quaternium-90 bentonite (2.75%) was conducted.[50] Biomicroscopic and peri-ocular examinations were performed on both eyes and the eyes were examined for functional signs prior to and after the first use and after the last use. Also, on the right eye of groups 1 and 2, a colormetric examination was performed on the cornea and conjunctiva, and a tear film break-up time measurement was performed. The contacts lenses of group 3 were examined before and after the test period. The eyeliner was applied once or twice per day on the upper and lower eyelids of both eyes; no other eye makeup was to be used during the test. Ocular irritation of slight to moderate intensity was reported in 2 subjects (1 with sensitive eyes and 1 with contact lenses). Ocular discomfort of slight intensity and short duration was reported in 1 subject wearing contact lenses. Palpebral irritation of slight to moderate intensity and long duration was reported in 1 subject with sensitive eyes and 1 wearing contact lenses. One subject with sensitive eyes was reported to have a conjunctival redness of slight intensity and long duration at the final examination of the eyes. The authors concluded that this product presented good ocular comfort, good ocular safety, and was well tolerated in subjects with sensitive eyes and contact lenses.

In a 1-week use study (n=25) of a mascara containing quaternium-90 bentonite (5.699%), there were no adverse reactions reported.[51]

Ocular-In Vitro

QUATERNIUM-90 BENTONITE

An eyeliner that contained quaternium-90 bentonite (2.75%) was predicted to be a weak irritant in a bovine cornea opacity/permeability (BCOP) assay.[52]

In 6 separate hen's egg tests-utilizing the chorioallantonic membrane (HET-CAM), 6 mascara products containing quaternium-90 bentonite (4.0275%) were predicted to be practically non-irritating.[53-58]

In an EpiOcular assay, a mascara containing quaternium-90 bentonite (5.924%) had an ET_{50} (estimated time to reduce cell viability by 50%) of 13.5 h.[59] It was concluded that this was "acceptable".

Sensitization

Dermal – Non-Human

STEARALKONIUM BENTONITE

Stearalkonium bentonite was not sensitizing to albino Hartley guinea pigs (n=20) when topically administered at 60% (in distilled water) during the induction phase and topically at 30% and 60% during the challenge phase.[25] There were no signs of sensitization at 24 and 48 h after the challenges. The test was conducted in accordance with OECD TG 406. The test sites were treated with 10% lauryl sodium sulfate in petroleum jelly prior to the induction phase.

QUATERNIUM-18 BENTONITE

A Draize test of quaternium-18 bentonite (0.1% in a physiological solution containing 2% Tween 80) was conducted using guinea pigs (n=12).[47] The test substance was administered intracutaneously at 0.05 mL on the first dose and at 0.01 mL for the remaining doses. The injections were administered 3 times per week for a total of 10 doses. Two weeks after the final induction, the challenge dose (0.05 mL) was administered. There was no evidence of hypersensitivity observed in any of the guinea pigs. Quaternium-18 bentonite was not a sensitizer under these test conditions.

Dermal - Human

There were no signs of irritation or sensitization in human repeated insult patch tests (HRIPT) of several products containing various alkonium clays; 4.3% was the highest concentration tested (Table 5).[60-64]

SUMMARY

This is a review of the available scientific literature and unpublished data assessing the safety of alkonium clays as used in cosmetics. Alkonium clays are derived from a group of phyllosilicate, layered, clay-based minerals, including montmorillonite, saponite, bentonite, and hectorite. These ingredients are grouped together because of the similar chemical structures, chemical composition, exchangeable ion type, and small crystal size of these minerals.

In cosmetics, these ingredients are reported to function as dispersing agents-nonsurfactant; emulsion stabilizers; viscosity increasing agents-nonaqueous.

Other alkonium clay-derived ingredients have been reviewed by CIR. Ammonium hectorites (disteardimonium hectorite, dihydrogenated tallow benzylmonium hectorite, stearalkonium hectorite, and quaternium-18 hectorite), hectorite, quaternium-18 bentonite, hectorite, bentonite, montmorillonite and other clays and earths were found to be safe as used.

Data on quaternium-18 bentonite were relied on to some degree for inference purposes; this includes new data (included in this Summary) and data from the previous report.

When alkonium bentonite clays with varying amounts of dimethyl dihydrogenated tallow quaternary ammonium chloride were dispersed in water at a level of 5% for 24 h, there was 10-20 ppm quaternary ammonium chloride present in the water phase; the saturation limit of dimethyl dihydrogenated tallow quaternary ammonium chloride is approximately 1500-2000 ppm.

Stearalkonium bentonite had the most reported uses at 388 including 385 leave-on uses and 3 rinse-off uses; it was reported to be used up to 6.5% in nail polish and enamel, 2.4% in lipstick, and 2.5% in eye shadow. Quaternium-90 bentonite was reported to be used in 64 leave-on products; it was reported to be used up to 6.1% in mascara and up to 6.1% in lipstick. It was confirmed by the Council that there were no reported uses of quaternium-90 bentonite in face powders and that a face and neck product reported to contain quaternium-90 bentonite was a lotion, not a powder.

The dermal LD_{50} of stearalkonium bentonite was >2000 mg/kg in rats.

The oral LD_{50} of stearalkonium bentonite was >5000 mg/kg in rats. The oral LD_{50} for benzyl-dimethyl-hydrogenated tallow ammonium montmorillonite clay was >5000 mg/kg in rats.

The reported inhalation LC_{50} for benzyl-dimethyl-hydrogenated tallow ammonium montmorillonite clay was >206 mg/L in rats when exposed for 1 h. There were no mortalities and no irreversible signs of toxicity observed in rats in an acute inhalation study of quaternium-18 bentonite at an average concentration of 5.7 mg/L with an exposure of over 4 h.

In a 28-day oral toxicity test of stearalkonium bentonite, the NOEL was 1000 mg/kg/d in rats.

Stearalkonium bentonite was not genotoxic to *S. typhimurium* (strains TA1535, TA1537, TA98, TA100, and TA102). It was cytotoxic at 316 µg/plate, without and with metabolic activation. In the tests without metabolic activation, cytotoxicity was also noted in several strains at concentrations of 31.6 and/or 100 µg/plate. In a micronucleus assay, stearalkonium bentonite was not clastogenic in mice when tested at doses up to 2000 mg/kg. In an Ames assay conducted on quaternium-18 bentonite in *S. typhimurium*, there were no signs of genotoxicity up to 1000 µg/plate with and without metabolic activation.

Stearalkonium bentonite was not irritating to intact or abraded skin of rabbits at 100%. The maximum non-irritating concentration for stearalkonium bentonite was 1.25% when injected intradermally and was not irritating when topically applied to the skin at a concentration of 60% in guinea pigs.

In a human patch test of a mascara containing quaternium-90 bentonite at 5.924%, it was concluded that the mascara was appropriate for consumer use.

In one study, stearalkonium bentonite was a severe ocular irritant when instilled into the eyes of rabbits at 100%. In another study, stearalkonium bentonite at 31-36 mg/ 0.1 mL was slightly irritating to rabbit eyes. Neither cornea nor irises were affected.

An eyeliner containing quaternium-90 bentonite at 2.75% was well-tolerated in a 4-week use test. In a 1-week use study of a mascara containing quaternium-90 bentonite at 5.699%, there were no adverse reactions reported.

An eyeliner that contained quaternium-90 bentonite at 2.75% was predicted to be a weak ocular irritant in a BCOP assay. In 6 HET-CAM assays, 6 mascara products containing quaternium-90 bentonite at 4.0275% were predicted to be practically non-irritating. In an EpiOcular assay, a mascara containing quaternium-90 bentonite at 5.924% had an ET_{50} of 13.5 h.

Stearalkonium bentonite was not sensitizing to guinea pigs when topically induced with a 60% solution and challenged topically with 30% and 60% solutions. There was no evidence of hypersensitivity observed in guinea pigs in a Draize Test of quaternium-18 bentonite at 0.1%.

There were no signs of irritation or sensitization in HRIPTs of several cosmetic products (e.g., mascara, 4.3%; foundation, 2.2%; lipstick, 1.452%; and spray leave-on product, 3.2% and 0.8%) containing various alkonium clays.

DISCUSSION

The CIR Expert Panel examined the available data on alkonium clays, which consists mostly of data on stearalkonium bentonite and quaternium-90 bentonite. The data included acute oral, dermal, and inhalation toxicity, oral repeated dose toxicity, genotoxicity, and dermal irritation and sensitization data. The data also include use studies and *in-vitro* assays of products used near the eyes. The Panel also considered the data available from safety assessments of previously reviewed alkonium clay ingredients, in particular quaterium-18 bentonite; new data on quaternium-18 bentonite were also evaluated. Because there were multiple genotoxicity assays with negative results from this and the previous hectorite and ammonium hectorite safety assessments, the Panel was comfortable that these ingredients are not carcinogenic.

Some of the components of these alkonium clays may be formed from plant-derived or animal-derived constituents and the clays used as cosmetic ingredients are derived from clays extracted from the ground. The Panel expressed concern regarding pesticide residues and heavy metals that may be present in the botanical-derived ingredients (e.g., quaternium-90-derived ingredients) as well as heavy metals that may be present in the clays. They stressed that the cosmetics industry should continue to use good manufacturing practices to sufficiently limit amounts of such impurities in ingredients before blending them into cosmetic formulations. Additionally, the Panel considered the dangers inherent in using animal-derived ingredients (e.g. quaternium-18/benzalkonium bentonite and hydrogenated tallowalkonium bentonite), namely the transmission of infectious agents. While tallow may be used in the manufacture of ingredients in this safety assessment and is clearly animal-derived, the Panel notes that tallow is highly processed, and tallow derivatives even more so. The Panel

agrees with determinations by the U.S. FDA that tallow derivatives are not risk materials for transmission of infectious agents.

These ingredients consist of assemblages of multiple macromolecules that are very tightly bound and interwoven, and as such, are completely insoluble in physiological fluids and are functionally particulates. However, it was noted that the manufacture of these ingredients includes cation exchanges conducted under mild conditions (e.g., low temperatures and neutral pH), suggesting that the cations could be released from these ingredients in cosmetic formulations. However, the quaternary ammonium compounds were shown to be very strongly adsorbed and stably bound within these alkonium clays under mild conditions. In previous safety assessments, the possible dissociates stearalkonium chloride and quaternium-18 were found to be safe as used, and benzalkonium chloride was found to be safe up to 0.1 %.

Tests for potential ocular irritation at the maximum concentration of use (6.1%) were not available for these ingredients, but there were use studies of a mascara and an eyeliner containing quaternium-90 bentonite up to 5.699% with negative results. These studies were sufficient to determine that ocular irritation is unlikely at maximum use concentrations.

The Panel discussed the issue of incidental inhalation exposure from aerosol suntan products because these ingredients are reportedly used at concentrations up to 3.2% in cosmetic products that may be aerosolized. There were no inhalation studies of these ingredients, but there were acute inhalation data on quaternium-18 bentonite and on dihydrogenated tallow benzylmonium hectorite, quaternium-18 hectorite, calcium silicate, and benzalkonium chloride in previous safety assessments. The Panel noted that 95%-99% of particles would not be respirable to any appreciable amount. Furthermore, particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the properties of these ingredients. 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.

CONCLUSION

The CIR Expert Panel concluded that the alkonium clay ingredients listed below are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating:

- benzalkonium montmorillonite*
- benzalkonium sepiolite*
- hydrogenated tallowalkonium bentonite*
- quaternium-18/benzalkonium bentonite*
- quaternium-90 bentonite
- quaternium-90 montmorillonite
- quaternium-90 sepiolite
- stearalkonium bentonite

*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 and functions of the alkonium clays in this safety assessment.[1]

Ingredient CAS No.	Definition	Function
Hydrogenated Tallowalkonium Bentonite	Hydrogenated Tallowalkonium Bentonite is the product of the reaction of hydrogenated tallowalkonium chloride and bentonite.	Viscosity increasing agent-aqueous
Quaternium-18/ Benzalkonium Bentonite	Quaternium-18/Benzalkonium Bentonite is a reaction product of bentonite and quaternium-18 and benzalkonium chloride.	Dispersing agent-nonsurfactant
Quaternium-90 Bentonite 226226-22-8	Quaternium-90 Bentonite is a reaction product of bentonite and quaternium-90.	Dispersing agent-nonsurfactant
Stearalkonium Bentonite 130501-87-0	Stearalkonium Bentonite is a reaction product of bentonite and stearalkonium chloride.	Dispersing agent-nonsurfactant
Benzalkonium Montmorillonite	Benzalkonium Montmorillonite is the reaction product of benzalkonium chloride and montmorillonite.	Dispersing agent-nonsurfactant; emulsion stabilizer; viscosity increasing agent-nonaqueous
Benzalkonium Sepiolite	Benzalkonium Sepiolite is the product obtained by the reaction of benzalkonium chloride and sepiolite.	Dispersing agent-nonsurfactant; emulsion stabilizer; viscosity increasing agent-nonaqueous
Quaternium-90 Montmorillonite	Quaternium-90 Montmorillonite is the product obtained by the reaction of quaternium-90 and montmorillonite.	Dispersing agent-nonsurfactant; emulsion stabilizer; viscosity increasing agent-nonaqueous
Quaternium-90 Sepiolite	Quaternium-90 Sepiolite is the product obtained by the reaction of quaternium-90 and sepiolite.	Dispersing agent-nonsurfactant; emulsion stabilizer; viscosity increasing agent-nonaqueous

Table 2. Data on related ingredients to the alkonium clays in this safety assessment.

Related ingredient	Summary data	Reference
Ammonium Hectorites - Quatemium-18 Hectorite, Disteardimonium Hectorite, Dihydrogenated Tallow Benzylmonium Hectorite, and Stearalkonium Hectorite	Safe as used; highest concentration of use: disteardimonium hectorite in makeup preparations at 28%. Single dose (acute) toxicity-oral :LD_{50} dihydrogenated tallow benzylmonium hectorite, 5.0 g/kg for rats; quaternium-18, >10 g/kg. Single dose (acute) toxicity-inhalation: LC_{50} dihydrogenated tallow benzylmonium hectorite, >5.2 mg/L for rats after 4 hours; aerosolized quaternium-18 hectorite was not toxic to rats at 202 mg/L after 1 h. Repeated dose toxicity: Stearalkonium hectorite was not dermally toxic to rabbits at concentrations of 12.5% to 50% over 3 weeks. Quaternium-18 hectorite administered to the skin of rabbits for 3 weeks was not toxic up to 50%. Genotoxicity: Stearalkonium hectorite was not mutagenic to *S. typhimurium* up to 1500 µL/plate or mouse lymphoma cells up to 500 µL/plate. Dermal irritation and sensitization: Stearalkonium hectorite did not cause erythema or edema to albino rabbits at 50% w/v. Quaternium-18 hectorite at 50% was not irritating to rabbits. Dihydrogenated tallow benzylmonium hectorite at 0.5 g in 0.5 mL saline was not irritating when administered to the intact and abraded skin of rabbits. Disteardimonium hectorite was not irritating to humans in 2 patch tests at 15%. Stearalkonium hectorite was not irritating or sensitizing to humans at 100%. Dihydrogenated tallow benzylmonium hectorite (concentration not provided) did not cause delayed contact hypersensitivity in albino guinea pigs. Quaternium-18 hectorite was not irritating or sensitizing up to 100% in HRIPTs. Ocular irritation: Stearalkonium hectorite was a minimal to mild ocular irritant to rabbits and humans. It was classified as a minimal to mild irritant in 3 Eyetex in vitro tests of products. Quaternium-18 hectorite was not an ocular irritant at 50% in rabbits and at 2 mg in humans. Dihydrogenated tallow benzylmonium hectorite at 0.5 g in 0.5 mL saline was practically nonirritating when administered to the eyes of rabbits.	[5]
Quaternium-18 Bentonite, Quaternium-18, and Quaternium-18 Hectorite	Safe as used; highest concentration of use: Review-quaternium-18 hectorite in eyeshadow, blushers, other makeup preparations, and suntan products, 10%; quaternium-18 in hair conditioners, 10%; quaternium-18 bentonite in lipstick, 10%. Re-review-quaternium-18 hectorite in other personal cleanliness products, 19%; quaternium-18 bentonite in mascara, 9%; quaternium-18 in hair tonics and dressings, 2%. Absorption, distribution, metabolism, and excretion: Quaternium-18 hectorite and bentonite are chemically, physically, and biologically inert. Quaternium compounds are poorly absorbed through the skin. Single dose (acute) toxicity-oral and percutaneous: Acute oral and percutaneous toxicity tests in animals indicate that all three compounds exhibit little or no systemic toxic effects. The oral LD_{50} of quaternium-18 bentonite was 8 g/kg in rats. Single dose (acute) toxicity-inhalation: Quaternium-18 hectorite was nontoxic in an acute	[2,4,5]

Table 2. Data on related ingredients to the alkonium clays in this safety assessment.

Related ingredient	Summary data	Reference
	inhalation study. Repeated dose toxicity- oral and dermal: Subchronic oral and dermal toxicity tests on quaternium-18 and quaternium-18 bentonite presented no evidence of systemic toxicity. There were no signs of toxicity in rats fed diets containing up to 25% quaternium-18 bentonite for 12 weeks. There was no evidence of local or systemic toxicity of quaternium-18 bentonite observed when administered to the depilated skin of rabbits under occlusion for 6 h/day for 90 days. Irritation and sensitization: All 3 quaternium compounds were considered to cause at most only slight irritation to animal skin. None has been reported to be skin sensitizing agents in animals. In clinical studies, quaternium-18 is practically nonirritating and nonsensitizing to the skin. Quaternium-18 hectorite and quaternium-18 bentonite can be classified as a nonirritating, "nonfatiguing," and nonsensitizing agent. Undiluted quaternium-18 bentonite at 0.5 g applied to both intact and abraded rabbit skin for 6 h/day for 5 consecutive days, and again after 10 days of rest for 5 more days elicited no reaction and was considered to be inert. Quaternium-18 bentonite at 0.1% was not sensitizing to guinea pigs. In an HRIPT of two eyebrow color preparation containing quaternium-18 bentonite at 4.1%, there was no evidence of skin irritation, "fatiguing," or sensitization observed. Ocular irritation: In ocular irritation studies in rabbits, all 3 ingredients have been shown to be at most mild irritants. Quaternium-18 Bentonite at 10% was not an ocular irritant in rabbits. Quaternium-18 hectorite exhibits no ocular irritation in humans. Phototoxicity: Quaternium-18 Hectorite does not present any adverse phototoxic or photoallergenic effects.	
Hectorite, Bentonite, Montmorillonite, Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Pyrophyllite, and Zeolite	Safe as used; highest concentration of use: Hectorite in skin cleansing preparations; Kaolin in other skin care preparations at 100%. Absorption, distribution, metabolism, and excretion: No absorption of aluminum and elevated levels of silicon were recorded in assayed plasma samples of dogs given magnesium trisilicate and zeolite orally; the urinary excretion of silica was 5.2% in males given 20 g of magnesium trisilicate. Single-dose (acute) toxicity-oral: oral LD_{50} of hectorite, >5 g/kg in rats; calcium silicate, 3400 mg/kg in rats; magnesium aluminum silicate, >50000 mg/kg in mice; zirconium silicate, > 200 g/kg in mice; kaolin, 149 g/kg in rats (death due to bowel obstruction); 15 natural zeolites, 10 g/kg in rats. Single-dose (acute) toxicity-dermal: The acute dermal LD_{50} was >3.5 g/kg for rabbits exposed to 4% magnesium aluminum silicate. Repeated dose toxicity-oral: In short-term oral toxicity studies, no adverse effects were seen in mice or rabbits dosed up to 5 g/kg magnesium aluminum silicate; beagle dogs and rats fed aluminum silicate had no renal lesions. Dogs and rats fed magnesium trisilicate for 4 weeks had polydypsia and polyuria, and all dogs had renal cortical lesions. Guinea pigs had renal lesions after 4 months of drinking magnesium trisilicate in their tap water. Rats fed 10% magnesium aluminum silicate had slightly elevated silicon levels of the spleen and dogs and rats fed 10% magnesium aluminum silicate had no negative responses in 90-day feeding studies. No lesions were found in rats dosed up to 1000 mg/kg for 104 weeks. Various zeolites added to the diets of pigs caused no adverse effects. Repeated dose toxicity-inhalation: Small primary neoplastic lesions were found in 2 rats exposed to a calcium silicate sample in an inhalation chamber. The mass of silicate measured in the lungs ranged from 0.1-0.8 mg. Lebrija and Leichester Attapulgite samples caused 1 peritoneal mesothelioma, one adenocarcinoma, and 3 bronchoalveolar hyperplasia and 2 mesotheliomas, 1 peritoneal mesothelioma, 1 malignant alveolar tumor and eight bronchoalveolar hyperplasia (inhalation route) in rats, respectively. Both samples contained long fibers. Moderate to extensive respiratory disease was noted in rats chronically exposed to synthetic zeolite A by inhalation methods. Irritation and sensitization: Hectorite was nonirritating to the skin of rabbits in a Draize primary skin irritation study. Magnesium aluminum silicate (4%) was a weak primary skin irritant in rabbits and had no cumulative skin irritation in guinea pigs. No gross effects were reported in any of these studies. Sodium magnesium silicate (4%) had no primary skin irritation in rabbits and had no cumulative skin irritation in guinea pigs. Ocular irritation: Bentonite caused severe iritis after injection into the anterior chamber of the eyes of rabbits. When injected intralamellarly, widespread corneal infiltrates and retrocorneal membranes were recorded. In a primary eye irritation study in rabbits, hectorite was moderately irritating without washing and practically nonirritating to the eye with a washout. A 4% solution of magnesium aluminum silicate and a 4% solution of sodium magnesium silicate caused minimal eye irritation in a Draize eye irritation test. Rats tolerated a single dose of zeolite A without any adverse reaction in the eye. Reproductive and developmental toxicity: Calcium silicate (250 to 1600 mg/kg) had no effect on nidation or on maternal or fetal survival in rabbits. Magnesium aluminum silicate (6000 mg/kg) had neither a teratogenic nor adverse effects on the mouse fetus. Female rats receiving a 20% kaolin diet exhibited maternal anemia but no reduction in birth weight of the pups was recorded. Type A zeolite produced no adverse effects on the dam, embryo, or fetus in either rats or rabbits at any dose level (74 or 1600 mg/kg). Clinoptilolite had no effect on female rat reproductive performance. Genotoxicity: In the *S. typhimurium* LT2 spot test (TA98, TA100, TA1535, TA1537, and	6

Table 2. Data on related ingredients to the alkonium clays in this safety assessment.

Related ingredient	Summary data	Reference
	TA1538) with or without metabolic activation, magnesium aluminum silicate and hectorite were found nonmutagenic. No increase mutation frequencies were seen in the *Salmonella* TA1530 or G-46 assay and no increase in recombinant activity in the *Saccharomyces* D3 assay treated with calcium silicate was observed. A subacute dose of 150 mg/kg of calcium silicate produced 3% breaks in bone marrow cells arrested in c-metaphase. In a metaphase spread of bone marrow cells, calcium silicate produced no increase in the number of aberrations compared to controls and in a dominant lethal assay did not induce any dominant lethal mutations. In primary hepatocyte cultures, the addition of attapulgite had no significant unscheduled DNA synthesis (UDS) response or modulated response to AAF (a positive control); attapulgite at 10 $\mu g/cm^2$ caused increases in UDS in rat pleural mesothelial cells. Zeolite particles (<10 µm*)* produced an increase in the percentage of aberrant metaphases, mostly chromatid breaks. Irritation and sensitization: Applications of 2 g of magnesium aluminum silicate to the skin of 2 humans daily for 1 week caused no effects. Occupational studies: In occupational exposure studies of mineral dusts, fibrosis and pneumoconiosis has been documented in workers involved in the mining and processing of aluminum silicate, calcium silicate, zirconium silicate, fuller's earth, kaolin, montmorillonite, pyrophyllite, and zeolite.	
Benzalkonium Chloride	Safe up to 0.1%; highest concentration of use: 0.1%; 0.5% in a liquid towelette Single dose (acute) toxicity-oral: Acute oral LD_{50} for rats dosed with benzalkonium chloride ranged from 342 to 525 mg/kg. Single dose (acute) toxicity-dermal: Of 96 mice receiving dermal applications of 6.5 and 50% benzalkonium chloride, 29 died within 72 h after application. Repeated dose toxicity-oral: In a subchronic toxicity study, benzalkonium chloride solutions were administered via stomach tube to 40 albino rats for 12 weeks (once/day) at dosages of 50.0 mg/kg (1:20 dilution) and 100.0 mg/kg (1:10 dilution). Two of 20 rats receiving the 100.0 mg/kg dosage died. In a chronic toxicity study, benzalkonium chloride (10.0%) was administered via stomach tube to 18 beagle dogs at dosages of 12.5, 25.0, and 50.0 mg/kg for 52 weeks (once daily). One of 6 dogs receiving 50 mg/kg dosages and 3 of 6 dogs receiving 25 mg/kg dosages died. Repeated dose toxicity-inhalation: No adverse effects were noted when rats and hamsters inhaled a conditioner containing 0.1% benzalkonium chloride over a period of 13 consecutive weeks (4 h/day). Irritation and sensitization-nonhuman: Benzalkonium chloride concentrations of 1.0%-50% induced reactions ranging from erythema to necrosis when applied to the skins of rabbits. In another study, 24-h applications of 1.0% to 10.0% benzalkonium chloride to the skins of rabbits resulted in severe induration. Benzalkonium chloride concentrations of 1.0% and 5.0% induced epidermal necrosis when applied (24-h exposure) to the skins of albino guinea pigs. Applications of 2.0% benzalkonium chloride to the skins (abraded and intact) of rabbits resulted in severe erythema (2-day application period). Slight erythema was noted 7 days after application. Applications of 1.0% benzalkonium chloride to the skins of white rats during a 2-month period caused hyperemia and necrosis. Following applications of 0.5% benzalkonium chloride to the skins of rabbits (24 h exposure), severe erythema, moderate edema, and eschar formation were observed. Benzalkonium chloride (0.5%) resulted in practically no skin irritation when applied to the skins of albino rabbits (24-h exposure). When 0.1% benzalkonium chloride was applied to the skins of rabbits (5-day contact period), slight erythema and necrosis were observed. These reactions were observed for 3 weeks post-treatment. Irritation and sensitization-human: Cutaneous reactions were observed in 2 of 399 dermatitis patients patch tested with benzalkonium chloride over a period of 64 months. In separate studies, primary irritant dermatitis was observed in 13 patients and 12 patients patch tested with 10.0% benzalkonium chloride (24-h exposure). In another study, erythema was observed in 33 of 70 leprosy patients patch tested with 2.5% benzalkonium chloride. Benzalkonium chloride concentrations of 0.5%, 1.0%, and 2.0% induced several pustular and/or bullous reactions in 26 of 55 patients (48-h exposures). The application of 17.0% benzalkonium chloride (24-hour period) to the skin of each of 21 subjects resulted in well-defined erythema (13 subjects). Confluent erythema and edema were noted in the skin of subjects tested with 5.0% and 2.5% benzalkonium chloride (12-h exposure). Results from a 21-day skin irritation study of a cream containing 0.1% benzalkonium chloride indicated essentially no cumulative irritation. A cream containing 0.1% benzalkonium chloride did not induce skin irritation or sensitization reactions in 101 subjects patch tested during a 6-week period (24-h exposures). Sensitization reactions were observed in 6 of 100 patients patch-tested with 0.07% benzalkonium chloride. The 6 patients also had positive reactions to 0.05%, 0.025%, and 0.01% benzalkonium chloride. Sixty-six of 2,806 patients were sensitive to 0.1% benzalkonium chloride. In another study, allergic reactions were observed in 9 of 142 patients patch tested with 0.1% benzalkonium chloride. Sensitization reactions were not observed in normal subjects patch-tested with 0.1% benzalkonium chloride. Ocular irritation: Benzalkonium chloride at 1% and 2.0% aqueous induced severe iritis and severe conjunctival injection, respectively, when instilled into the conjunctival sac of rabbits twice daily for 7 days. Benzalkonium chloride (0.3%) induced minimal ocular irritation when instilled once into the eyes of rabbits. Single instillations of 0.1% benzalkonium chloride into the conjunctival sac of albino rabbits did not cause ocular	[7,8]

Table 2. Data on related ingredients to the alkonium clays in this safety assessment.

Related ingredient	Summary data	Reference
	irritation. The instillation of 0.1% benzalkonium chloride into the conjunctival sacs of rabbits 5 times daily for 1 week resulted in corneal damage. The instillation of 0.01% benzalkonium chloride into the conjunctival sacs of rabbits (5 min-6-h period) resulted in cornea1 damage. Four hours after the instillation of 0.5%, 1.0%, and 10% benzalkonium chloride, cornea1 damage was noted in rabbits and guinea pigs. The ocular administration of 0.5%, 1.0%, and 2.0% solutions twice daily for 7 days caused conjunctival damage in rabbits. Following the daily administration of 0.007% and 0.1% benzalkonium chloride for 2 weeks, retinal detachment was observed in pigmented but not albino rabbits. In in vitro intraocular toxicity studies, the exposure of rabbit corneas to benzalkonium chloride concentrations ranging from 0.0001% to 0.01% resulted in cornea1 damage. Exposure periods ranged from 2 min (0.01%) to 110 min (0.0001%). The longest exposure was 180 min (0.0065%). Slight conjunctival hyperemia was observed in 1 of 51 human subjects who received ocular instillations of 0.02% benzalkonium chloride. Reproductive and developmental toxicity: The instillation of 100 or 208 mg/kg of aqueous benzalkonium chloride into the vaginas of pregnant rats resulted in sternal defects in the offspring. Genotoxicity: Benzalkonium chloride was not mutagenic to *S. typhimurium* (strains TA1535, TA1536, TA1537, and TA1538) and *E. coli* (strains B/r WP2 her^+ and WP2 her^-) in microbial test systems making up the ret-assay in combination with reverse mutation systems. Mutagenic activity also was not demonstrated in reversion assays involving *S. typhimurium* (strains TA1535, TA1536, TA1537, and TA1538) and, in the ret-assay, with *Bacillus subtilis* (strains H17 Ret^+ and M45 Rec^-). In the plate incorporation assay, benzalkonium chloride was not mutagenic to *S. typhimurium* (strains TA98, TA1538, TA1537, and TA100). In the *E. coli* DNA polymerase assay benzalkonium chloride induced repairable DNA damage in strains W3110 (pol A+) and p3478 (pol A-). Carcinogenicity: The dermal application of 8.5% and 17% benzalkonium chloride to rabbits and mice did not result in tumor formation or systemic toxic effects, but did produce ulceration and inflammation at the application sites.	
Stearalkonium Chloride	Safe as used; highest concentration of use: review, 5%, re-review, 7%. Single dose (acute) toxicity-oral: The oral LD_{50} of stearalkonium chloride in rats ranged from 0.5-1.25 g/kg. Repeated dose toxicity-oral: In mice, an LD_{50} value of 0.760-0.113 g/kg was reported in a 7-day oral study. Irritation and sensitization: In single application dermal studies with concentrations of up to 25%, stearalkonium chloride produced minor irritation in rabbits. A repeated insult patch test with a 1% aqueous solution of stearalkonium chloride on 50 human subjects showed the material to be neither a primary irritant nor a sensitizer. A single 48-hour patch test with challenge 2 weeks later indicated that 20% stearalkonium chloride was not a sensitizer. Ocular irritation: In acute eye studies in rabbits, a 25% solution of stearalkonium chloride was a severe irritant. Concentrations of 1.25% and less were slightly and transiently irritating to the rabbit eye.	[4,9]

Table 3. Chemical and physical properties of stearalkonium bentonite.

Property	Value	Reference
Stearalkonium bentonite		
Density/Specific Gravity @ 25 ºC	330-480	[25]
Melting Point ºC	>390	[25]
Boiling Point ºC	>500	[25]
Water Solubility g/L @ 20 ºC	$<0.04x10^{-3}$	[25]
log K_{ow} @ 25˚C	5.87 (estimated)	[25]

Table 4. Frequency of use according to duration and exposure of alkonium clays.[36-39]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Quaternium-90 bentonite		Quaternium-90 montmorillonite		Quaternium-90 sepiolite		Stearalkonium bentonite	
Total/range	**64**	**0.41-6.1**	**NR**	**0.4-0.8**	**NR**	**1.6-3.2**	**388**	**0.051-6.5**
Duration of use								
Leave-on	64	0.41-6.1	NR	0.4-0.8	NR	1.6-3.2	385	0.19-6.5
Rinse-off	NR	0.63	NR	NR	NR	NR	3	0.051
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type[a]								
Eye area	31	0.41-6.1	NR	NR	NR	NR	7	0.19-2.5
Incidental ingestion	16	6.1	NR	NR	NR	NR	63	0.5-2.4
Incidental Inhalation-sprays	2[b]	NR	NR	0.8[d]	NR	3.2[d]	1[c]	NR
Incidental inhalation-powders	2[b]	NR	NR	NR	NR	NR	NR	NR
Dermal contact	35	0.41-4	NR	0.4-0.8	NR	1.6-3.2	25	0.19-2.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	0.46-0.5	NR	NR	NR	NR	300	0.015-6.5
Mucous Membrane	16	6.1	NR	NR	NR	NR	65	2.4
Baby	NR	NR	NR	NR	NR	NR	NR	NR

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.

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.

[a] 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.

[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[d] In this case, quaternium-90 montmorillonite and quaternium-90 sepiolite are sold as a trade name mixture. This mixture is used in an aerosol suntan product.

Table 5. HRIPTs of cosmetic products containing alkonium clays.

Ingredient(s); product; concentration	n; details	Results	Reference
Quaternium-90 Bentonite; mascara; 4.3%	102; Modified Draize test with 9 administrations (3x/week). Patches on the scapula were removed after 24 h. After a 2-week rest, the test substance was administered to a naïve site and observed at 24, 48, and 72 h after removal.	There were no reactions to indicate irritation or sensitization during the induction or challenge phases.	60,61
Quaternium-90 Bentonite; foundation; 2.2%	102; 9 administrations (3x/week). Patches (1"x1") were allowed to volatize for several minutes prior to placement on the scapula and were removed after 24 h. After a 2-week rest, the test substance was administered to a naïve site and observed at 24, 48, and 72 h after removal. After a 2-week rest, the test substance was administered to a naïve site and observed at 24 and 72 h after removal.	There was no indication of irritation or allergic contact sensitization.	63
Stearalkonium Bentonite ; lipstick; 1.452%	100; test substance was applied to a patch pad and remained in the open air for 15-20 min before administration to the infrascapular area of the back or the upper arm for 24 h. There were 9 administrations in the induction phase.	There were no signs of irritation or sensitization.	64
Quaternium-90 Sepiolite and Quaternium-90 Montmorillonite in a spray leave-on product; 3.2% and 0.8%, respectively[a]	56; The test substance (0.2 mL) was administered to the upper back on 0.75" x 0.75" occlusive patches and left for 24 or 48 h for 9 administrations.	There were no signs of irritation or sensitization.	62

[a] Quaternium-90 montmorillonite and quaternium-90 sepiolite (at 0.8% and 3.2%, respectively) in this case are a trade name mixture.

REFERENCES

1. Nikitakis, J and Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 15 *ed*. Washington, DC: Personal Care Products Council, 2014.

2. Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of quaternium-18, quaternium-18 hectorite, and quaternium-18 bentonite. *International Journal of Toxicology*. 1982;1(2):71-83.

3. Andersen, FA. Final report onthe safety assessment of stearalkonium hectorite. *International Journal of Toxicology*. 2000;19(Suppl. 2):91-98.

4. Andersen, FA. Annual review of cosmetic ingredient safety assessments - 2001/2002. *International Journal of Toxicology*. 2003;22(Suppl. 1):1-35.

5. Becker, LC, Bergfeld, W, Belsito, D, Hill, R, Klaassen, C, Liebler, D, Marks Jr, J, Shank, R, Slaga, T, Snyder, P, and Andersen, F. Safety assessment of ammonium hectorites as used in cosmetics. *International Journal of Toxicology*. 2013;32(Suppl. 4):33S-40S.

6. Elmore, AR and Cosmetic Ingredient Review Expert Panel. Final report on the safety assessemt of aluminum silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magneium silicate, zirconium silicate, attapulgite, bentonite, fuller's earth, hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate, montmorillonite, pyrophyllite, and zeolite. *International Journal of Toxicology*. 2003;22(Suppl. 1):37-102.

7. Andersen, FA. Annual review of cosmetic ingredients safety assessments 2005/2006. *International Journal of Toxicology*. 2008;27(Suppl. 1):77-142.

8. Elder, RL. Final report on the safety assessment of benzalkonium chloride. *Journal of the American College of Toxicology*. 1989;8(4):589-626.

9. Elder, RL. Final report on the safety assessment of stearalkonium chloride. *Journal of the American College of Toxicology*. 1982;1(2):57-69.

10. European Chemicals Agency (ECHA). Information on Chemicals-Benzyl-dimethyl-hydrogenated tallow ammonium montmorillonite clay. http://echa.europa.eu/information-on-chemicals. Last Updated 2015.

11. World Health Organization (WHO). Bentonite, kaolin, and selected clay minerals. Geneva, World Health Organization. 2005. http://www.who.int/ipcs/publications/ehc/ehc_231.pdf. pp. 1-196.

12. Brindley, GW and Hofmann, R. Orientation and packing of aliphatic chain molecules on montmorillonite. *Clays and Clay Minerals*. 1962;9:246-256.

13. Jordan, JW. Organophilic bentonites. I. Swelling in organic liquids. *Journal of Physical and Colloid Chemistry*. 1949;53(2):294-306.

14. Lagaly, G, Fernandez-Gonzales, M, and Weiss, A. Problems inlayer-charge determination of montmorillonites. *Clay Minerals*. 1976;11:173-187.

15. Lagaly, G. Characterization of clays by organic compounds. *Clay Minerals*. 1981;16:1-21.

16. Organization for Economic Cooperation and Development (OECD). SIDS [Screening Information Data Set] Initial Assessment Profile: Orangoclays catagory. *Screening Information Data Set Initiantion Assessment Meetings (SIAM) 25*. 10-17-2007. http://webnet.oecd.org/hpv/UI/handler.axd?id=4946e752-d9c2-4272-a862-f102906260e9#page=5&zoom=auto,-91,842

17. Grim, RE and Wahl, FM. Bentonite. Parker, SP. In: *McGraw-Hill encyclopedia of the geological sciences*. 2 ed. New York: McGraw-Hill; 1988:32-33.

18. Bates, RE and Jackson, JA. Glossary of geology. 3 *ed*. Alexandrea, VA: American Geological Institute, 1987.

19. Alvarez, A. Sepiolite: Properties and uses. Singer, A and Galan, E. In: *Palygorskite-Sepiolite: Occurrences, Genesis and Uses*. New York: Elsevier; 1984:253-287.

20. Garben, PW and Bates, RL. Geology of the Nonmetallics. New York: Metal Bulletin, Inc., 1984.

21. Callen, RA. Clays of the palygorskite-sepiolite group: Deposition, environment, age and distribution. Singer, A and Galan, E. In: *Palygorskite-sepiolite: Occurrencesm Genesis and Uses*. New York: Elsevier; 1984:1-37.

22. Clarke, GM. Special clays. *Industrial Minerals*. 1985;September:25-51.

23. Renjun, Z. Sepiolite clay deposits in South China. Singer, A and Galan, E. In: *Palygorskite-sepiolite: Occurrences, Genesis and Uses*. New York: Elsevier; 1984:251-252.

24. Elementis Specialties. 2015. Alkonium clays - free quaternary ammonium chloride. Unpublished data submitted by Personal Care Products Council.

25. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Public report: stearalkonium bentonite. Sidney, Australia, Department of Health and Ageing. 2013. http://www.nicnas.gov.au/chemical-information/new-chemical-assessments. Report No. STD/1414. pp. 1-28.

26. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Public Report: STD/1531: Organoclay 5 in Garamite 1958, STD/1532: Organoclay 6 in Garamite 7305 (INCI Name: benzalkonium montmorillonite, STD/1533: Organoclay 7 in Garamite 7303 (INCI Name quaternium-90 montmorillonite), STD/1542: Organoclay 8-Quaternary ammonium compounds, benzyl(hydrogenated tallow alkyl)dimethyl, salts with bentonite (INCI Name: hydrogenated tallowalkonium bentonite), and STD/1543: Organoclay 9 - Tixogel VZ/VA-V. Sidney, Australia, NICNAS. 2015. Report No. STD/1531-33, 42 & 43. pp. 1-18.

27. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Public Report: STD/1527: organoclay 1 in Garamite 1958, STD/1528: Organoclay 2 in Garamite RXG-7253/RXG-1753, STD/1529: Organoclay 3 in Garamite 7305 (INCI Name benzalkonium sepiolite), and STD/1530: Organoclay 4 in Garamite 7303 (INCI Name: Quaternium-90 sepiolite). Sidney, Australia, NICNAS. 2015. Report No. STD/1527-1530. pp. 1-18.

28. Kanoles C. Letter to Carol Eisenmann, Personal Care Products Council concerning the CIR Safety Assessment of Alkonium Clays. 8-6-2015. Unpublished data submitted by the Personal Care Products Council.

29. Koh, S-M. New understanding of clay minerals. CASM-Asia Meeting at Bandung 2006: State-of-the-Art of Science and Technology to Protect the Environment and People. 11-27-2006. Bandung, Indonesia.

30. Bish, DL and Guthrie Jr, GD. Mineralogy of clay and zeolite dusts (exclusive of 1:1 larger silicates). Chapter: 4. Guthrie Jr, GD and Mossman, BT. In: *Reviews in Mineralogy*. Vol. 28. Chelsea, MI: Book Crafters; 1993:139-184.

31. Grim, RE. Clay mineralogy. 2 *ed*. New York: McGraw-Hill, 1968.

32. Smectite clay chemistry. 3 *ed*. Carol Stream, IL: Allured Publishing Corp, 2002.

33. Fiore, S, Cavalcante, F, Medici, L, Ragone, PP, Lettino, A, Barbaro, M, Passariello, B, and Quaresima, S. Trace element mobility in shales: Implicaitons on geological and environmental studies. Proceedings of Euroclay 2003. 2003.

34. Parks, WR. Occupational lung disorders. London: Butterworths, 1982.

35. Koshi, K, Kohyama, N, Myojo, T, and Jukuda, K. Cell toxicity, hemolytic action and clastogenic activity of asbestos and its substitutes. *Industry Health*. 1991;29(2):37-56.

36. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients; *FDA Database*. Washington, DC, FDA. 2016.

37. Personal Care Products Council. 8-27-2015. Updated Concentration of Use by FDA Product Category: Alkonium Clays. Unpublished data submitted by Personal Care Products Council.

38. Personal Care Products Council. 1-6-2015. Concentration of Use by FDA Product Category: Alkonium Clays. Unpublished data submitted by Personal Care Products Council. 1 pages.

39. Personal Care Products Council. 12-3-2015. Updated Concentration of Use by FDA Product Category: Alkonium Clays. Unpublished data submitted by Personal Care Products Council.

40. Personal Care Products Council. 9-16-2015. Comments on the Draft Report Prepared for the September 2015 CIR Expert Panel Meeting: Safety Assessment of Alkonium Clays as Used in Cosmetics. Unpublished data submitted by Personal Care Products Council.

41. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

42. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;14(11):24-27. http://www.spraytechnology.com/index.mv?screen=backissues.

43. Rothe H. Special aspects of cosmetic spray safety evaluation. 2011. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C.

44. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 8-28-2011;205(2):97-104. PM:21669261.

45. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. http://ec.europa.eu/consumers/cosmetics/cosing/. Last Updated 2014. Date Accessed 1-14-0015.

46. Odom, IE. Smectite clay minerals: Properties and uses. *Philosophical Transactions of the Royal Society of London.Series A, Mathamatical and Physical Sciences*. 1984;311(1517):391-409.

47. Elementis Specialties. 2015. BENTONE® 34 (INCI: Quaternium-18 Bentonite): Toxicity dossier. Unpublished data submitted by Personal Care Products Council.

48. Personal Care Products Council. 2015. BENTONE® 34 (INCI: Quaternium-18 Bentonite): Toxicity dossier. Unpublished data submitted by Personal Care Products Council.

49. Anonymous. 2013. Summary of a 48-hour patch test of a mascara containing Quaternium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

50. Peritesco. 2009. Ocular acceptability study of an eye liner (containing 2.75% Quaternium-90 Bentonite) performed during 4 weeks under ophthalmological control. Unpublished data submitted by Personal Care Products Council.

51. Anonymous. 2013. Summary of a 1 week use study of a mascara Quatemium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

52. EVIC France. 2008. Assessment of the irritant potential by the isolated calf cornea method (BCOP) (eyeliner containing 2.75% Quatemium-90 Bentonite). Unpublished data submitted by Personal Care Products Council.

53. Consumer Product Testing Co. 2011. The hen's egg test- utilizing the chorioallantoic membrane (HET-CAM) of a mascara containing 4.0275% Quaternium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

54. Consumer Product Testing Co. 2012. The hen's egg test- utilizing the chorioallantoic membrane (HET-CAM) of a mascara containing 4.0275% Quaternium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

55. Consumer Product Testing Co. 2013. The hen's egg test- utilizing the chorioallantoic membrane (HET-CAM) of a mascara containing 4.0275% Quaternium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

56. Consumer Product Testing Co. 2014. The hen's egg test- utilizing the chorioallantoic membrane (HET-CAM) of a mascara containing 4.0275% Quaternium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

57. Consumer Product Testing Co. 2014. The hen's egg test- utilizing the chorioallantoic membrane (HET-CAM) of a mascara containing 4.0275% Quaternium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

58. Consumer Product Testing Co. 2015. The hen's egg test- utilizing the chorioallantoic membrane (HET-CAM) of a mascara containing 4.0275% Quaternium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

59. Anonymous. 2013. Summary of an epiocular assay of a mascara containing Quaternium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

60. Anonymous. 2010. Summary of an HRIPT of a mascara containing Quatemium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

61. Clinical Research Laboratories Inc. 2010. Summary of an HRIPT of a mascara containing 4.3% Quaternium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

62. Clinical Research Laboratories Inc. 2014. Summary of an HRIPT of a spray leave-on body product containing 0.8% Quaternium-90 Montmorillonite and 3.2% Quaternium-90 Sepiolite. Unpublished data submitted by Personal Care Products Council. 1 pages.

63. Consumer Product Testing Co. 2011. Repeated insult patch test of a foundation containing 2.2% Quaternium-90 Bentonite. Unpublished data submitted by Personal Care Products Council.

64. TKL Research Inc. 3-11-2015. Human repeated insult patch study: Lipstick containing 1.452% Stearalkonium Bentonite. Unpublished data submitted by Personal Care Products Council.