Safety Assessment of Quaternium-18 and Quaternium-18 Bentonite as Used in Cosmetics

Status:	Re-Review for Panel Consideration
Release Date:	August 22, 2019
Panel Meeting Date:	September 16-17, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Priya Cherian, Scientific Analyst/Writer
Date: August 22, 2019
Subject: Re-Review of the Safety Assessment of Quaternium-18 and Quaternium-18 Bentonite

The CIR Expert Panel first reviewed the safety of Quaternium-18 and Quaternium-18 Bentonite in 1982. The Panel concluded that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration, as described in that report (identified as *quat092019orig* in the pdf). In 2003, after considering new studies and updated use data on these ingredients, the Panel published the re-review summary in which it is stated that the Panel determined not to re-open the safety assessment (*quat092019RR1sum*). It should be noted that Quaternium-18 Hectorite was also included in the 1982 safety assessment and previous re-review. However, Quaternium-18 Hectorite is not included in this current re-review because it was recently (2013) part of a separate assessment (Safety Assessment of Ammonium Hectorites as Used in Cosmetics). In that assessment, Quaternium-18 Hectorite was determined to be safe as used in cosmetics in the present practices of use and concentration.

The minutes from the Panel deliberations of the 2003 re-review are included herein (*quat092019min_RR1*). Minutes from the deliberations of the original report are unavailable.

Because it has been at least 15 years since the first re-review summary was published, in accord with CIR Procedures, the Panel should again consider whether the safety assessment of Quaternium-18 and Quaternium-18 Bentonite should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1995 forward. No relevant published data were found; however unpublished data provided by the Council regarding Quaternium-18 Bentonite were provided (*quat092019data*), and summaries of these data have been included (*quat092019newdata*). Some of the data provided were already included in the original report (acute and subacute oral toxicity, subchronic dermal toxicity, dermal irritation, allergenicity, and ocular irritation data); therefore, that information has not been included in this re-review.

Also included with this submission are current and historical use data (*quat092019usetbl*). Since the initial re-review was considered, frequency and concentration of use have decreased for both ingredients. According to VCRP data, Quaternium-18 and Quaternium-18 Bentonite were used in 90 and 221 total formulations, respectively, in 2001. In 2019, the VCRP data indicate that Quaternium-18 is used in 61 formulations, and Quaternium-18 Bentonite is used in 199 formulations (*quat092019FDA*). In 2001, the maximum concentration of use for Quaternium-18 Bentonite was reported to be 9% in leave-on products, while in 2018 maximum concentration of use was reported to be 2.5% in leave-on products (*quat092019conc*). A decrease in concentration of use was also reported for Quaternium-18; the reported maximum concentrations of use in 2001 and 2018 were 2% and 0.95%, respectively.

A data profile is included indicating the data from the original (1982) report and the new data (*quat092019prof*). If, upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

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Quaternium-18 and Quaternium-18 Bentonite Data Profile – September 2019 – Priya Cherian																																
	Use				Toxico-kinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	New Rpt	Old Rpt	Method of Mfg	Impurities	log P	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Quaternium-18	X	O		O					O			O									O	O			O			O		
Quaternium-18 Bentonite	X	O		XO					O	X	O	O				X					O	O		O	O			O		

* "X" indicates that new data were available in this category for the ingredient; "O" indicates that data from the original assessment were available

Quaternium-18 and Quaternium-18 Bentonite Re-Review Search Strategy – September 2019 -- Priya Cherian

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Quaternium-18	61789-808	yes	no	yes	no	yes	no	no	no	no	no	no	yes	no	no	no	no	no	no
Quaternium-18 Bentonite	1340-69-8 68953-58-2	yes	yes	no	no	yes	no	no	no	no	no	no	no	no	no	no	no	no	no

Search Strategy

-Search from 1995 – present
-INCI names, CAS numbers
-dermal, irritation, sensitization, toxicity, inhalation, manufacture

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (https://scifinder.cas.org/scifinder)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org

- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/

- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/

- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/phytochem/search
- Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- European Medicines Agency Herbal Medicines - http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – http://www.ifraorg.org/
- Research Institute for Fragrance Materials (RIFM)

Minutes for Quaternium-18 and Quaternium-18 Bentonite – November 2001

A CIR Final Report with the following conclusion on these ingredients was published in 1982: On the basis of the available information presented in this report, the Expert Panel concludes that Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite are safe as cosmetic ingredients in the present practices of use and concentration.

Dr. Marks said that his Team determined that the safety assessment does not need to be reopened.

Dr. Belsito said that Quaternium-18 is being used in hair sprays and that inhalation data are not available. With this in mind, he said that it should be pointed out that the particle size is so large that it would not be respirable, and, therefore, inhalation toxicity data are not needed.

Dr. Bergfeld recommended the inclusion of this statement in the discussion section on this ingredient family in the Annual Review.

The Panel unanimously concluded that the CIR Final Safety Assessment on Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite should not be reopened.

Regarding the proposed Annual Review document on ingredients that have been considered for re-review, Ms. Fise strongly recommended that the Panel have an opportunity to routinely review the text for each ingredient/ingredient family entry after the Panel meeting in which these ingredients are considered.

Dr. Andersen said that the commitment in the revised CIR Procedures is to insure a 90-day public comment period.

Ms. Fise wanted to know if the Panel will have an opportunity to see the document before it is announced for public comment, to make sure that all concerns expressed have been captured.

Dr. Bergfeld said that the report would have to be reviewed by the Panel prior to announcement.

Dr. Andersen noted that CIR Tentative Reports generally are not reviewed by the Panel prior to announcement; however, the Panel has an opportunity to review the report before it is issued as a Final Report. He added that if it is the Panel's preference that the document be reviewed prior to announcement, this could be implemented.

Dr. Bergfeld said that because the re-review process is new to CIR, review of the document prior to announcement is advisable at this point in time. She added that after the re-review process has been in operation for a period of time, it could then proceed in a manner that is consistent with the usual CIR review process.

The Panel agreed that the document should be reviewed by the Panel prior to public announcement.

Current and historical frequency and concentration of use of Quaternium-18 and Quaternium-18 Bentonite

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Quaternium-18				**Quaternium-18 Bentonite**			
	2019[1]	**2001[2]**	**2018[3]**	**2001[2]**	**2019[1]**	**2001[2]**	**2018[3]**	**2001[2]**
Totals*	**61**	**90**	**0.46 – 0.95**	**0.1 - 2**	**199**	**221**	**0.15 – 2.5**	**0.8 - 9**
Duration of Use								
Leave-On	*18*	*27*	*0.46*	*0.1 – 2*	*199*	*218*	*0.15 – 2.5*	*0.8 - 9*
Rinse-Off	*43*	*63*	*0.76 – 0.95*	*1 – 2*	*NR*	*3*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	1	NR	NR	72	70	NR	4 - 9
Incidental Ingestion	2	NR	NR	0.7	108	138	NR	5
Incidental Inhalation-Spray	15[a]	1; 3[a]	0.46[a]	0.1 – 2[a]	3[a]; 1[c]	1[a]	2.5[a]	5[a]
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	0.29[b]	NR
Dermal Contact	1	16	NR	NR	86	79	0.29 - 1	0.8 - 6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	0.6[d]	NR
Hair - Non-Coloring	58	68	0.46 – 0.95	0.1 – 2	3	NR	2.5	NR
Hair-Coloring	NR	1	NR	NR	NR	NR	NR	NR
Nail	NR	5	NR	NR	2	NR	0.15 – 0.25	NR
Mucous Membrane	2	1	NR	0.7	108	141	NR	5
Baby Products	NR	NR	NR	NR	NR	NR	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 these products are sprays, but it is not specified whether the reported uses are sprays.

[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.

[c] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, there fore the information is captured in both categories

[d] Formulated as a spray

NR – no reported use

REFERENCES

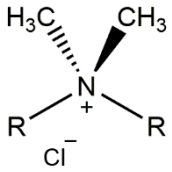
1. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2019. Voluntary Cosmetic Registration Program (VCRP) - Frequency of Use of Cosmetic Ingredients. *(Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" ; received January 31, 2019)*. College Park, MD.

2. Andersen F.A. (ed). Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite. *Int J Toxicol* 2003;22:25-27.

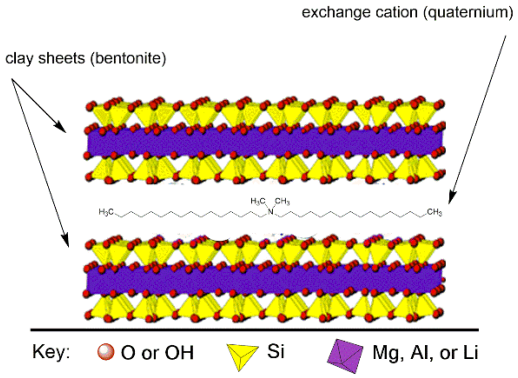
3. Personal Care Products Council. 2018. Council Concentration of Use by FDA Product Category: Quaternium-18 Compounds. *(Unpublished data submitted by the Personal Care Products Council on October 2, 2018)*.

New Data – Quaternium-18 and Quaternium-18 Bentonite

Structures



Quaternium-18 – wherein R represents hydrogenated tallow fatty radicals.



Quaternium-18 Bentonite

Impurities

Quaternium-18 Bentonite

According to a toxicity dossier, Quaternium-18 Bentonite contained an average amount of < 3% crystalline silica as an impurity.[1]

Acute Toxicity

Inhalation

Quaternium-18 Bentonite

Five male and five female Sprague-Dawley rats were exposed to Quaternium-18 Bentonite for 262 minutes in a stainless steel and glass chamber.[1] The time-weighted average exposure concentration was determined to be 5.7 mg/L. No mortality or irreversible signs of toxicity were seen in any animal after a four hour exposure.

Genotoxicity

Quaternium-18 Bentonite

An Ames test was performed using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 with and without metabolic activation.[1] The test substance, Quaternium-18 Bentonite, was used at concentrations of 17, 50, 167, 500, and 5000 µg/plate. The test substance was considered to be non-genotoxic.

REFERENCES

1. Elementis Specialties. 2015. BENTONE ® (INCI: Quaternium-18 Bentonite): Toxicity dossier. (Unpublished data submitted on August 7, 2015.)

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: August 7, 2015

SUBJECT: Alkonium Clays: Information on Quaternium-18 Bentonite

Kanoles C. Letter to Carol Eisenmann, Personal Care Products Council concerning the CIR Safety Assessment of Alkonium Clays.

Elementis Specialties. 2015. BENTONE® 34 (INCI: Quaternium-18 Bentonite): Toxicity dossier.

ELEMENTIS
SPECIALTIES

August 6, 2015

Carol J. Eisenmann, Ph.D., D.A.B.T.
Senior Toxicologist, Science Department
Personal Care Products Council
1101 17th Street, N.W., Suite 300
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Phone: 202 331-1770
eisenmannc@personalcarecouncil.org

Re: CIR Safety Assessment of Alkonium Clays

Dear Dr. Eisenmann,

This is in response to your request for additional information regarding the safety assessment of Alkonium Clays that is being performed by the Cosmetic Ingredient Review (CIR) Board.

Enclosed please find information regarding the toxicological data, chemical and physical properties, and impurities and that are applicable to Alkonium Clays used as cosmetic and personal care ingredients. The enclosed documents consist of the following:

- Toxicity Dossier for BENTONE® 34 (INCI name Quaternium-18 Bentonite), containing results for the following tests:
  - Acute Oral Toxicity
  - Skin (Dermal) Irritation
  - Eye (Ocular) Irritation
  - Allergenicity
  - Subacute Oral Toxicity
  - Subchronic Dermal Toxicity
  - Acute Inhalation Toxicity
  - Ames Mutagenicity

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We can also provide the following information regarding the physical and chemical characteristics, including impurities, of Alkonium Clays in general, and BENTONE® 34 in particular.

- For Alkonium Clays, the ratio of cations (i.e. "quats") used vs the clay varies, depending on both the type of cation and the type of clay. Exact ratios for a given product are proprietary and confidential. Typically, the cation falls within the range of 20 – 40% and the clay falls within the range of 60 – 80%.
- The median particle size of BENTONE® 34 was measured and determined to be 28 um.
- BENTONE® 34 contains crystalline silica as an impurity. The average amount is < 3%.
- Dermal penetration studies are not available for BENTONE® 34. As noted in the CIR Safety Assessment of Ammonium Hectorites, the charge properties and large molecular weights of these clay-like ingredients would preclude significant dermal penetration. A similar conclusion would be expected for Alkonium Clays.

An extensive toxicological data set provides confirmation that the Alkonium Clay BENTONE® 34 is non-toxic, non-irritating, non-sensitizing and non-mutagenic. Alkonium Clays have a large particle size (well outside the nanomaterial range). As noted in the CIR Safety Assessment of Ammonium Hectorites, the charge properties and large molecular weights of these clay-like ingredients would preclude significant dermal penetration. A similar conclusion would be expected for Alkonium Clays.

Alkonium Clays are very similar to the Ammonium Hectorites that were previously reviewed by CIR. The types of cations (quats) used are similar or identical. The clays used, bentonite and hectorite, are smectite-family clays. They can therefore be expected to have similar characteristics in terms of toxicological profile, lack of dermal penetration, etc.

The information provided support the use of Alkonium Clays as ingredients in cosmetic and personal care applications. Please do not hesitate to contact us if you need any additional information.

Sincerely,

Christ Kanoles
Senior Product Stewardship Manager

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BENTONE® 34

TOXICITY DOSSIER

Product: BENTONE® 34
INCI Name: Quaternium-18 Bentonite

Toxicological Studies

Acute Oral Toxicity

Result: Acute oral LD50 greater than 8,000 mg/kg. No animals died during the observation period of the study.

Method: Twenty adult albino rats, balanced by weight and sex distribution were used for the study. The product was suspended in cottonseed oil, and administered via gastric lavage.

Skin (Dermal) Irritation

Result: The Primary Irritation Index is 0. Therefore, the test article is not irritating. The detailed assessment is as follows:

Redness: x = 0
Edema: x = 0
Eschar: x = 0

Method: Draize test. Ten rabbits were used for the study.Topical applications were made on the depilated intact and abraded skin. Contact was maintained six hours daily for five successive days, ten days without treatment were allowed to intervene, and the applications were then repeated for five days.

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Eye (Ocular) Irritation

Result — The Primary Irritation Index is 0. The reactions in the test article eyes were completely negative. Therefore, the test article is classified as non- irritating for eyes and eye mucous membranes.

Method — Draize test. Ten rabbits were used in the study. For the study, the test article was instilled into the eyes of the rabbits in the form of a 10 percent suspension in physiological saline solution. Only single doses were administered. Observations for irritation of the cornea, iris and conjunctiva were scored.

Allergenicity

Result — No evidence of hypersensitivity was seen in the test animals. Therefore, the test article is classified as non-allergenic to guinea pigs.

Method — Draize test. Twelve guinea pigs were used for the study. For the study, the product was administered intracutaneously in the form of a 0.1 percent suspension in physiological saline solution containing 2 percent Tween 80 to facilitate dispersion. Three injections were given each week until a total of ten doses were administered. The first dose consisted of 0.05 mL, and the subsequent doses were 0.1 mL. After a lapse of two weeks, the challenging or test dose of 0.05 mL of the suspension was injected. Ratings were made of the maximum diameters and heights of the wheals and of the erythemal reactions at the sites of both the sensitizing and test doses, according to the scoring system of Draize.

Subacute Oral Toxicity

Result — No significant impairment of growth, food utilization, hemoglobin level, or red or white blood cell count was observed, when fed at dietary levels as high as 25 percent. A slight reduction in efficiency of food utilization (EFU) at the highest test level may be explained by generally lower nutrient intake. Gross autopsies and weights of the livers and kidneys gave no indication of a toxic reaction at these test levels.

Method — Sixty rats were divided into five groups of twelve rats each, balanced with respect to sex, litter and body weight. Over the course of the 12 week feeding study the rats were fed diets consisting exclusively of nutritionally adequate basal ration alone, or supplemented with 1, 5 or 25 percent of Bentone 34. An additional group was fed a diet of 25 percent bentonite clay principally to control the effect of the reduced caloric value at this high displacement level of the basal diet.

The animals were housed individually, with diet and water supplied ad libitum. Weekly records were kept of food consumption, body weight and changes in physical appearance and behavior. Pairs of rats of each sex were selected at the end of the 12 week period for hematological examination. Post-mortem examinations were made of all of the animals, and liver and kidney weights were recorded.

Subchronic Skin Toxicity

Result

No evidence of a toxic reaction, either local or systemic, was found to result from the chronic topical exposure to the test article or the control article.

Method

Twenty healthy young adult albino rabbits were depilated over the backs and rumps in areas of approximately 15 x 18 cm. For not less than six hours each week day over a period of 90 days this area of the skin of each rabbit was maintained in contact with 0.5 gm of moistened sample. Ten rabbits were treated with Bentonite 34 (test article) and ten with bentonite clay (control group).

The condition of the skin was observed at the end of each exposure period and the start of the following one. The scoring system for rating irritation of the skin was that described by Draize. At the end of the 90 day test period, blood hemoglobin levels were determined, complete blood counts were made, and gross autopsies were performed. The livers, kidneys and a portion of the skin from the treated areas were then submitted for histopathological examination.

Acute Inhalation Toxicity

Result

No mortality or irreversible signs of toxicity were seen in any animal after a four hour exposure to a test atmosphere containing 5.7 mg/L (average actual concentration) of the test article. Animals were observed for 14 days following exposure to the test article.

Method

Five male and five female Sprague-Dawley rats were used in the study. The animals were exposed to the test article for 262 minutes in a 309 L stainless steel and glass chamber. Total airflow was maintained at a rate of 65 L/minute. The time weighted average exposure concentration was determined to be 5.7 mg/L. Particle size of the test article was determined to be > 10 um (Mass Median Aerodynamic Diameter), with 30% of collected particles $\leq$ 10 um in size. Average chamber temperature was 21 °C. Average chamber relative humidity was 51%.

Ames Salmonella /E. Coli Mutagenicty Test

Result	The product is considered to non-mutagenic in this Salmonella typhimurium reverse mutation assay. Using the same test conditions, there was no detectable genotoxic activity associated with the sample under testing, neither in the presence or absence of the S9 enzyme activation, using the Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 at the following concentrations: • Plate Incorporation: 10, 30, 100, 300, 3000 microgram/plate. Toxicity test using Salmonella typhimurium TA 100 showed no toxicity to the bacteria at the following concentrations: • 17, 50, 167, 500, 1667 and 5000 microgram/plate. Precipitation occurred at 5000 micrograms/plate.
Method	Ames Test – OECD 471 – Bacterial Reverse Mutation Test

Christ Kanoles
Senior Product Stewardship Manager
August 6, 2015

5

Final Report on the Safety Assessment of Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite

Quaternium-18 is a mixture of quaternary ammonium chloride salts. Quaternium-18 Hectorite and Bentonite are the reaction products of Quaternium-18 with clays. These compounds are poorly absorbed through the skin. Acute oral and percutaneous toxicity tests in animals indicate that they exhibit little or no systemic toxic effects. Subchronic oral and dermal toxicity tests on Quaternium-18 and Quaternium-18 Bentonite present no evidence of systemic toxicity.

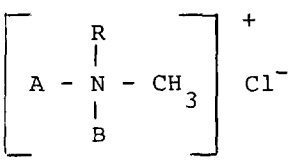
These compounds are only slightly irritating to the animal skin, and are not sensitizing agents. In ocular irritation studies all three compounds have been shown to be at most mild irritants.

Quaternium-18 has been found to be practically nonirritating and nonsensitizing to human skin. Quaternium-18 Hectorite is classified as a nonirritating, and nonsensitizing agent. It does not present adverse phototoxic or photoallergenic effects. Quaternium-18 Bentonite is not an irritating or sensitizing agent to the human skin and does not induce ocular irritation in humans.

On the basis of the available information, it is concluded that Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite are safe as cosmetic ingredients in the present practices of use and concentration.

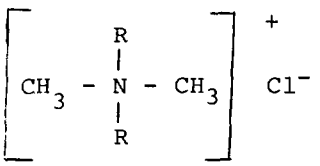
CHEMICAL PROPERTIES

Quaternium-18: Quaternium-18 is a mixture of quaternary ammonium chloride salts conforming to the general formula:



where R = hydrogenated tallow fatty radicals having a chain length distribution of C_{18}(65%), C_{16}(31%) and C_{14}(4%) and where A,B = $-CH_3$, $-CH_3$, or $-CH_3$, R or R,R. Tallow is fat derived from ovine or bovine adipose tissue that is comprised principally of fatty acid glycerides.[1]

Quaternium-18 is predominantly (90–100%) a dimethyl, ditallow quaternary nitrogen compound as shown below. From 0–5% trimethyl monotallow ammonium chloride, or monomethyl tritallow ammonium chloride may also be present.[1,2]



Quaternium-18 is produced by hydrolysis, ammonolysis, and hydrogenation of tallow. Quaternization is completed by alkylation with CH_3Cl.[2]

Quaternium-18 Clays: Quaternium-18 Hectorite and Quaternium-18 Bentonite are the ion exchange addition products of Quaternium-18 and Hectorite or Bentonite clays, respectively.[1,2] The production of these two ingredients is described in U.S. Patent No. 2,531,427.[3] The clay material is reacted with an aqueous slurry of the quaternary compound. When the adduct precipitate is washed and dried, the final product is ready.

Bentonite is a native hydrated colloidal aluminum silicate clay which has absorptive properties. It is a Smectite (Montmorillonite) mineral clay with a general formula of $Al_2O_3 \cdot 4SiO_2 \cdot H_2O$; magnesium can displace some of the constituent aluminum. Although the composition of Bentonite varies regionally, a typical analysis is as follows: SiO_2 (64.32%), Al_2O_3 (20.74%), Fe_2O_3 (3.03%), Na_2O (2.59%), MgO (2.30%), CaO (0.52%), FeO (0.46%), K_2O (0.39%), SO_3 (0.35%), TiO_2 (0.14%), and H_3PO_4 (0.01%).

Hectorite is a Smectite mineral clay with a general formula of $3\ MgO \cdot 4SiO_2 \cdot H_2O$; lithium can displace some of the constituent magnesium. While the composition of Hectorite varies according to its regional origin, a typical analysis is as follows: SiO_2 (56.30%), MgO (26.00%), F^- (3.47%), Na_2O (2.70%), CaO (2.50%), Li_2O (1.51%), CO_2 (1.30 percent), Al_2O_3 (0.1%), and FeO (0.05%).[1,2,4]

Physical Properties

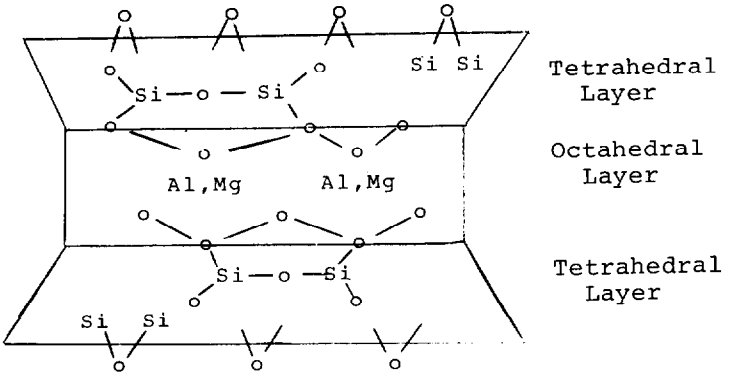
Quaternium-18: As a result of its polar nature, Quaternium-18 exhibits hydrophilic properties. A paste-like substance, it is soluble in both water and isopropyl alcohol.[2]

Quaternium-18 Clays: Quaternium-18 Hectorite and Bentonite are relatively inert organo-clay compounds that are heat stable up to 500°C and resist base or acid attacks over a pH range of 3–11. When added to other compounds, they tend to render them more stable. Both are hydrophobic agents but can stabilize emulsions by inhibiting oil-water phase separation. These ingredients have a gel-like consistency that display thixotropic properties. When the gel is

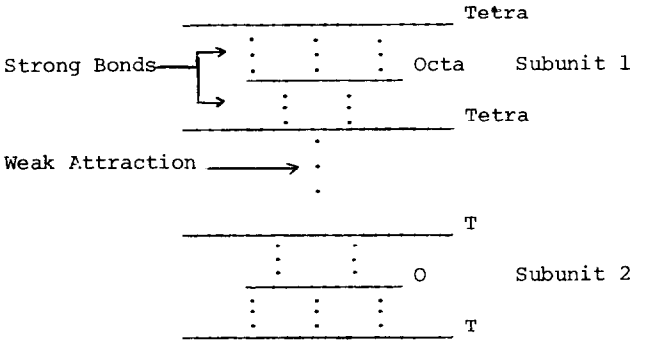
disturbed, it tends to become more fluid, which adds aesthetic value to certain cosmetic products.[5,6]

The Quaternium-18 clays are expansible in water, methanol, ethanol, isopropanol, sorbitol, glycerine and acetone.[4]

Hectorite and Bentonite Clays: Silicate clays are composed of three-layer subunits. Each trilaminar subunit consists of two tetrahedral layers sandwiching an octahedral layer. The former layers contain silicon and oxygen in tetrahedral configuration; the latter contains aluminum (Bentonite) or magnesium (Hectorite) and oxygen in octahedral configuration. Oxygen molecules located along the faces of the octahedral subunit are shared with the tetrahedral subunits. Thus, intralayer binding within a given subunit is covalent and strong.



Oxygen molecules also project from the free surfaces of the tetrahedral layers. Interlayer attraction between subunits is by Van der Waals forces and is relatively weak. The individual subunits are free to slide over one another so as to give the clay a slick texture.



Hectorite and Bentonite are swelling clay minerals in which the interlayer spacing between adjacent subunits is in dynamic equilibrium with the amount of available moisture. Since the interlamellar forces are weak, water molecules can readily permeate the interlayer spaces. Dry clay has a spacing between subunits of 9.5 Å. At 50% relative humidity, the spacing is 12.5–15 Å; at 100% saturation, it reaches 18 Å. Many water-miscible organic compounds (methanol, ethanol,

isopropanol, sorbitol, glycerine and acetone) can also expand these clays in the same way.

The combination of weak interlayer forces and the percent hydration with such other factors as the presence of interlaminar cations gives these clays their gel-like nature. Changes in hydration or electrolyte composition of the cosmetic medium being used or the application of shearing stresses can cause the gel to become more fluid (thixotropy). Removal of such perturbations promotes regelation of the formulation.[5]

Reactivity

Quaternium-18 Hectorite and Bentonite are inert, chemically stable materials. They are both pH and heat stable under the normal conditions of cosmetic use.[5,6]

Analytical Methods

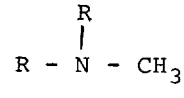
Four techniques are described for the determination of quaternary ammonium chloride salts.[2]

1. *Free sodium chloride content.* The sample is ashed and titrated with $AgNO_3$ (0.1 N).
2. *Quaternary chlorides.* The sample is dissolved in isopropanol and titrated with $AgNO_3$ (0.1 N) in the presence of dichlorofluorescein (0.1% w/v of isopropanol) indicator.
3. *Free amine value.* The sample is melted (if solid) and dissolved in isopropanol to which bromphenol blue (0.2% w/v of isopropanol) indicator has been added. The solution is then titrated with isopropanol-HCl (0.1 N).
4. *Acid value—percent amine hydrohalide.* The sample is melted (if solid) and dissolved in isopropanol to which phenolphthalein indicator has been added. The solution is then titrated with isopropanol-KOH (0.1 N).

Impurities

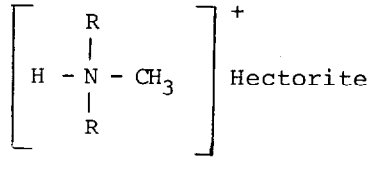
Three groups of impurities are associated with Quaternium-18 Hectorite and Bentonite. These are listed below in descending order of predominance (concentrations not reported).[2]

1. Methyl, ditallow amine



where R is as before.

2. Methyl, ditallow ammonium Hectorite



3. Sodium chloride, NaCl

No reference has been found pertaining to the use of preservatives or antioxidants with these compounds.

PURPOSE AND FREQUENCY OF USE IN COSMETICS

In a variety of cosmetic products, the Quaternium-18 compounds are employed to maintain suspensions during application (that is, to ensure uniform dispensing of the active ingredients) and to inhibit compaction or settling. They are added to lotions and creams for both thermal and physical emulsion stabilization (that is, to inhibit phase separation). The thixotrophic properties of these ingredients add aesthetic value to lipsticks and makeups.[7]

Table 1 presents categories and concentrations of use of the Quaterniums.[8] The cosmetic product formulation computer printout which is made available by the Food and Drug Administration (FDA) is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations (1979). Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the true, effective concentration found in the finished product; the effective concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

Quaternium-18 has been reported to be used in 20 products (concentration range of 0.1–10%); it is employed in hair conditioners and rinses and in nail polish and enamels. Quaternium-18 Bentonite is used (concentration range of 0.1–10%) in eight personal cleanliness and lipstick products. Quaternium-18 Hectorite is used (concentration range of 0.1–10%) in over 140 eyeshadows and mascaras, face powders, blushers and rouges, lipsticks, nail polish and enamels, and various gels, creams, and lotions. These products, along with the approximate Quaternium concentration used in each of them, are listed in Table 1.[8]

Quaternium-based formulations can come into contact with the face (makeups, rouge, blushers, powders); the eyelids (mascara, eyeshadows); the lips (lipsticks); the hair (conditioners, rinses); the nails (polish, enamels); the entire skin (gels, creams, lotions); and the hands (when the product is applied to other areas of the body) (Table 1).

The frequency with which Quaternium-containing products are applied may vary from occasionally (hair conditioners and rinses) to daily (eyeshadow, mascara, lipsticks). The duration of application can range from seconds (hair conditioners and rinses) to all day (creams, lotions, mascara, powder, lipstick); these products may remain in contact with the body for extended periods of time (nail polishes and enamels), and occasional or daily use may extend over many years (Table 1).

TABLE 1. Product Formulation Data.[a]

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Quaternium-18 Hectorite		
Eyeshadow	>5–10	3
	>1–5	9
	>0.1–1	5
Mascara	>1–5	9
	≤0.1	3
Other makeup preparations	>1–5	1
Blushers (all types)	>5–10	1
	>0.1–1	4
Face powders	>0.1–1	1
Foundations	>0.1–1	1
Lipstick	>1–5	7
	>0.1–1	1
Makeup bases	>1–5	1
	>0.1–1	1
Rouges	>1–5	5
	≤0.1	1
Other makeup preparations	>5–10	1
	>1–5	1
Nail polish and enamel	>1–5	26
	>0.1–1	55
	≤0.1	1
Other personal cleanliness products	>0.1–1	4
Suntan gels, creams, and lotions	>5–10	1
Quaternium-18		
Hair conditioners	>5–10	1
	>1–5	4
Rinses (noncoloring)	>0.1–1	4
Nail polish and enamel	>0.1–1	11
Quaternium-18 Bentonite		
Lipstick	>5–10	1
Other personal cleanliness products	>0.1–1	7

[a]Data from Ref. 8.

BIOLOGICAL PROPERTIES

General Effects

Dimethyl, dioctadecyl ammonium chloride (DDAC), has been evaluated in an in vivo percutaneous absorption study. Ten mg of the ^{14}C-radiolabeled (30 μCi) compound was applied in an open patch test to a 5 × 8 cm area on the dorsal surface of each of four rabbits. All excreta (urine, feces, expired CO_2) were collected for 72 hours. Approximately 89% of the delivered radioactivity was recovered: 88% (skin test site); 0.29% (cage wash); 0.27% (CO_2); 0.20% (other skin); 0.16% (feces); and 0.15% (urine). These data indicate that DDAC does not appreciably penetrate the skin.[9]

The same investigator who conducted the study just described confirmed his

results in an in vitro study which used skin from the abdomen of human infants; DDAC did not penetrate this material.[9]

The FDA has proposed that Bentonite clay be granted GRAS status as a direct food ingredient. Upon oral administration, very little (if any) Bentonite clay is absorbed. As much as 3% in the diet of experimental animals had no negative effects.[10]

Animal Toxicology

Acute Studies

Oral toxicity

Acute oral toxicity studies have been conducted on all three Quaternium compounds and on a variety of cosmetic formulations in which they appear.

Quaternium-18: A 5% aqueous dispersion of this ingredient was administered to male rats by intragastric intubation. Six rats each received 5 g/kg of the dispersion and four received 10 g/kg. No deaths occurred in either group. The LD50 of the dispersion was estimated to be in excess of 10 g/kg. The estimated LD50 of Quaternium-18 is somewhat greater than 0.5 g/kg, since the dispersion contained only a 5% concentration of this ingredient.[11]

In another study, a 4% aqueous dispersion was given orally in doses of 5, 10, and 20 ml/kg to groups of six rats. None of the rats died during the 14-day observation period that followed dosing. The LD50 was reported as greater than 20 ml/kg of the 4% dispersion, which allows the LD50 of the ingredient to be calculated as greater than 0.8 g/kg.[12]

A 75% aqueous suspension administered orally to rats at two dose levels (doses or number of rats were not specified) was described as having an LD50 of 7000 mg/kg. This reflects an oral LD50 of the ingredient of 5250 mg/kg.[13]

Doses varying from 1 g/kg to 10 g/kg of a 70% solution of Quaternium-18 in isopropanol were given orally to 98 rats. The doses below 5 g/kg were further diluted with isopropanol. The resultant LD50 was 6.35 g/kg. (This LD50 included the effect of the isopropanol, which was not tested separately).[14]

Quaternium-18 Hectorite: In an acute oral toxicity study, five groups of five rats each were given a 50% (w/v) aqueous suspension by gavage; the doses ranged from 1.25–20 g/kg. No deaths occurred during the 14-day observation period. The oral LD50 of the suspension is greater than 20 g/kg or greater than 10 g/kg of the ingredient.[15]

Products that include relatively small amounts of the ingredient were tested for oral toxicity. When an eyeshadow formulation containing 10 percent Quaternium-18 Hectorite was evaluated in rats, the product's LD50 was calculated to be greater than 5 g/kg.[16] Three personal cleanliness formulations were each given to 10 rats in 1 g/kg oral doses; for each formulation tested, the LD50's were greater than 1 g/kg.[17]

When a fingertip powder blusher (10% Quaternium-18 Hectorite) was administered orally to 10 rats via stomach intubation at a single dose of 25 g/kg, no mortalities resulted. The LD50 of the product was reported as greater than 25 g/kg.[18]

Quaternium-18 Bentonite: This ingredient was given orally, as a suspension in cottonseed oil in doses of 8 g/kg, to twenty rats. No deaths occurred in two weeks following dosing. The suspension was difficult to manipulate, so no higher doses were given. Available data indicate that the LD50 is greater than 8 g/kg.[14]

Skin irritation

Quaternium-18: An aqueous dispersion containing 5% of this ingredient was applied to one intact and one abraded area of the skin of each of six rabbits. To each area, 0.5 ml was applied and covered by a gauze patch which was removed after 24 hours; then the remaining dispersion was washed off. At 24 and 72 hours after application, the reaction was graded; no irritation was found.[11]

Tested with a similar procedure, a 4% aqueous dispersion gave comparable results.[12]

A more concentrated (75%) sample of the ingredient was tested according to the Draize method. The Primary Irritation Index (PII) was calculated to be 1.92 out of a possible maximum of 8. Examination of the scores showed that erythema had increased at the 72-hour observation period, indicating that there had been a delayed irritant reaction.[19]

Another commercial 75% aqueous dispersion of Quaternium-18 was studied at concentrations of 2%, 5% and 10%. The actual concentrations of the ingredient were 1.5, 3.7, and 7.5%. Patches containing 0.05 g of the suspensions were applied to the skin of rabbits and allowed to remain there for 21 days, after which the patches were removed and the irritation at the sites graded. The dispersion was determined to be a mild irritant at the concentrations used.[13] This same product was also tested at 10 percent to determine its ability to irritate mucosa; 0.2 ml of the commercial product was applied to the penile mucosa of rabbits. Grading of the irritation gave a score of 0.43 out of a possible maximum of 4, showing this product had a mild ability to irritate mucosa.[13]

Quaternium-18 Hectorite: A Federal Hazardous Substance Act skin irritation test was conducted with this compound, using a dose of 0.5 g of a 50% suspension in water on each of six rabbits. When it came in contact with intact or abraded skin, this material did not produce any irritation.[15]

Quaternium-18 Bentonite: The undiluted ingredient was applied in quantities of 0.5 g to both intact and abraded rabbit skin. After contact was maintained for six hours per day for five consecutive days, there were 10 days of rest and then five more days of exposure. No reaction was found, and the test material was considered to be inert.[14]

Skin sensitization

Quaternium-18 Bentonite: The ability of this ingredient to produce allergic reaction on the skin of guinea pigs was studied by intracutaneous injection. Twelve guinea pigs were given an initial injection of 0.05 ml of the test sample (0.1% in physiological saline). Then, three additional injections of 0.1 ml were made each week for the next three weeks, after which there was a two-week rest period. At the end of this time, challenge doses of 0.05 ml were injected. Increased reaction to the challenge dose over the induction dose would have indicated a sensitization. However, the challenge doses gave less reaction than the induction dose, indicating no sensitization.[14]

Eye irritation

Quaternium-18: One-tenth of a milliliter of a 5% aqueous dispersion of this ingredient was instilled in one eye, the other remaining untreated as a control; six rabbits were used. Cornea, iris and conjunctiva were all found free of irritation during the 72-hour observation period.[11]

A 4% dispersion of the ingredient was tested by the same procedure. No cor-

neal or iridial irritation occurred, but some conjunctival irritation, which disappeared with time, was reported.[12]

A product containing a 75% suspension of the ingredient was also tested in the rabbit eye. The product was diluted to 10% (making the test material a 7.5% dispersion), and 0.1 ml of this was placed in the conjunctival sac. Readings were made at 24 and 48 hours after instillation. The eye irritation score was reported to be 11.7 out of a possible 110, making the 7.5% dispersion a minimal irritant.[13]

Quaternium-18 Hectorite: A rabbit eye irritation test was performed according to the Draize method with 0.1 ml of a 50% aqueous suspension; no irritation was produced.[15]

Quaternium-18 Bentonite: Instillation of 0.1 ml of a 10% suspension in physiological saline was made into one eye of each of 10 rabbits. Twenty-four hours after instillation, the "test eyes" were completely negative for irritation.[14]

Acute inhalation toxicity

Quaternium-18 Hectorite: An inhalation toxicity study evaluated a one-hour exposure of 10 rats to a mist containing the ingredient. Quaternium-18 Hectorite was mixed with isopropyl myristate to facilitate spraying (concentration not stated). One hundred forty-three grams of the mixture were atomized in the one-hour period; the nominal concentration was calculated to be 202 mg/l. In the 14 days following exposure, no toxic manifestations were noted and no deaths occurred.[15]

Subchronic Studies

Oral toxicity

Quaternium-18: This material was fed at varying concentrations to guinea pigs for 12 days. Uniform doses of 10 ml/kg were administered daily to two animals at each concentration. The lowest dose level that produced signs of toxicity appeared to be 1 g/kg/day.[13] Quaternium-18 was also fed to dogs and rats at subacute dietary levels of 2800 ppm for 90 days. No abnormalities were found in food consumption, body weight, reaction, mortality, or urinalysis, or in hematologic, blood chemistry, gross pathologic, or histopathologic studies.[13]

Quaternium-18 Bentonite: Groups of 12 weanling rats were fed diets containing 1%, 5%, or 25% of the ingredient for 12 weeks. Two similar groups were fed the basic diet and served as controls. The gain in weight per unit of diet consumed was practically the same for groups consuming up to 5%, while a reduction of food efficiency occurred in the 25% group. At the end of 12 weeks, hematology, organ weights, gross pathology, and micropathology were essentially the same in all groups, and there was no indication that any subchronic oral toxicity was produced by the ingredient.[14]

Dermal toxicity

Quaternium-18 Hectorite: Aqueous suspensions containing 50%, 25%, 12.5%, or 0.0% of this ingredient in quantities of 4 g/kg were applied to the exposed skin of rabbits three times a day, five days per week for three weeks. Each application, spread over at least 20% of the body surface, was allowed to remain on the skin for two hours, after which the remaining material was washed off, the skin dried, and the next dose applied. Six rabbits were used for each concentration, three with intact skin and three with the skin abraded. During the study,

general health, appetite, and activity did not differ among the groups. Weight gain, hematological elements, and gross and micropathology were similar in all groups. Some animals, including controls, had inflammatory lesions in the heart, brain, liver, kidney, and lung. These were attributed not to the test materials, but to protozoan infection, which was reported to be common in rabbits obtained from commercial suppliers. The local effects on the skin consisted of mild drying and scaling of the upper layers in the early days of the study. Continued exposure did not produce involvement of the deeper layers.[15]

Quaternium-18 Bentonite: Ten rabbits were depilated (15 × 18 cm) on their dorsa and exposed under occlusion to 0.5 g of Quaternium-18 Bentonite for six hours per day for 90 days. Ten control animals were also used. Exposure sites were scored for irritation according to the Draize criteria at the end of such exposure and at the beginning of the next. Hematological and gross pathological findings were normal for both groups. Micropathology revealed minor liver and kidney abnormalities in both experimental and control groups; chronic protozoan infection was implicated. No evidence of local or systemic toxicity of Quaternium-18 Bentonite was found.[20]

Clinical Assessment of Safety

Skin Irritation and Sensitization

Quaternium-18

This ingredient was investigated for its skin irritating and sensitizing characteristics on 25 men and 25 women (Caucasian) varying in age from 18 to 35. The repeated insult, occluded patch test was employed. Patches (1.5 in^2) were saturated with sample (7.5%, unspecified diluent) and applied for 24 hours to the volar aspect of the arm; 24 hours elapsed between each scoring and application, which totalled 15 per person. Ten days after the last induction exposure, a 24-hour challenge application of sample was made to each subject. The results and accompanying analysis can be found in Table 2. Six out of the 50 subjects reacted 13 times to the 750 induction exposures. Only two of the 13 reactions were level-2 reactions. Two of the 50 subjects reacted to the challenge exposure; there were no other reactors. The mean primary skin irritation index (PSI) for all test subjects was calculated to be 0.26 out of a maximum of 8. The

TABLE 2. Repeated Insult and Skin Sensitization Human Studies—Quaternium-18.[a]

		No. of subjects	*No. of applications*	*Intensity of reactions*				
				4	*3*	*2*	*1*	*0*
Primary Skin Irritation	Male	25	375	0	0	2	7	366
	Female	25	375	0	0	0	2	373
	Total	50	750	0	0	2	9	739
Skin Sensitization	Male	25	25	0	0	1	0	24
	Female	25	25	0	0	1	0	24
	Total	50	50	0	0	2	0	48

[a]Data from Ref. 13.

mean skin sensitization (SS) index (calculated in the same manner as the PSI) for the 50 subjects was 0.08 out of a maximum of 8. The number of subjects tested for potential sensitization to Quaternium-18 is suboptimal. Although the number of subjects used in the testing program is suboptimal, the ingredient was classified by the investigator as "practically nonirritating and nonsensitizing to the skin."[13]

Quaternium-18 Hectorite

Pure Ingredient: This compound was evaluated for primary irritancy, "fatiguing" ability (potential cumulative effects of repeated application), and/or skin sensitizing capacity. The study included 50 humans exposed 15 times each to undiluted sample under occluded patch (3 × 3 cm) and once each to a challenge application. No visible skin changes were reported in any subject. According to the author, Quaternium-18 Hectorite may be considered nonirritating, "nonfatiguing," and nonsensitizing to the skin.[15]

Ingredient in Cosmetic Formulations: An eye shadow (10% Quaternium-18 Hectorite) was tested for skin reaction on 50 women. The undiluted product was applied to the intended area of use twice daily for 30 days. Each woman was examined five times (Weeks 0, 1, 2, 3, and 4) by a dermatologist; no evidence of skin irritation or sensitization was found.[15] Three other formulations containing Quaternium-18 Hectorite (1.0–5.0%) were tested for skin irritation and sensitization. Twelve panelists were exposed to sample (0.5 g of undiluted product) under semiocclusive patch conditions for 23 hours per day for three weeks. The products were evaluated as being slightly irritating.[15] When these same three products were applied (0.5 g) three times per week for three weeks to 175 subjects under occlusive patch conditions for 24 hours, they were found to be nonsensitizing.[15] A fingertip powder blusher (10% Quaternium-18 Hectorite) was evaluated for primary irritation and sensitization and for phototoxicity and photocontact allergenicity. A population of 209 human subjects was exposed to the product under occlusive patch test conditions (modified Draize–Shelanski–Jordan Test). No indication of skin irritation or sensitization was found.[15]

Twenty-five male and female panelists were exposed to the fingertip powder blusher (10% Quaternium-18 Hectorite) in a photopatch test. Two $\mu l/cm^2$ of sample were applied to two different skin sites which were then covered with standard patches for 24 hours. At patch removal, one treated site and a new third site were exposed for 30 seconds to light originating from a Krohmeyer hot-quartz spot-lamp and filtered through window-glass. The irradiated sites were scored immediately for irritation. The entire protocol was repeated four additional times. Challenge applications to previously untreated sites were made 12 days after the last induction exposure; one untreated and two treated sites were used. Twenty-four hours after challenge, one treated site and one untreated site were irradiated as before. The sites were examined and scored at 24 and 48 hours. No reactions were noted; the product was reported to exhibit no evidence of phototoxicity or photoallergy.[12]

Quaternium-18 Bentonite

The repeated insult patch test was employed to test two eyebrow color preparations (4.1 or 4.0% active ingredient) on 50 human subjects. No evidence of skin irritation, "fatiguing," or sensitization was found for either product.[14] A clinical test of Quaternium-18 Bentonite at a concentration greater than 4.1 per-

cent would have been desirable, since one cosmetic formulation contains > 5–10% of the ingredient.

Eye Irritation: Quaternium-18 Hectorite has been screened for its capacity to cause ocular irritation in the human. Two preparations were used: undiluted, finely divided powder (20 g of powder dissolved in 100 ml of physiological saline) and 20 g of powder suspended in 100 ml of corn oil. The undiluted powder (2 mg) was applied directly in the conjunctival sac of one eye in each of 10 subjects. Panelists were asked to describe any adverse symptoms they experienced immediately following instillation of the sample and the eyes were examined immediately and after 1 and 24 hours. All subjects reported a "sand-like" feeling in the treated eye, but without stinging or pain. The two diluted compounds were tested simultaneously, one sample per eye of each of ten panelists. Upon instillation, both eyes were held shut for one minute; the subjects were then asked to open their eyes and describe any abnormal ocular sensations. No one reported feeling pain in either eye, though (like the undiluted powder) the saline-dissolved sample gave a "sand-like" feeling to the eye. All treated eyes were examined (in an unspecified manner) at 0, 1, and 24 hours. No obvious damage to the eye was observed.[15]

SUMMARY

Quaternium-18 is a mixture of quaternary ammonium chloride salts. Quaternium-18 Hectorite and Bentonite are the reaction products of Quaternium-18 and Hectorite or Bentonite clays, respectively. All three ingredients are used in cosmetic formulations at concentrations ranging from 0.1% to 10%. Cosmetics containing these compounds may come into contact with all body surfaces and may be used on a daily basis over extended periods of time.

Quaternium-18 Hectorite and Bentonite are chemically, physically, and biologically inert. Quaternium compounds are poorly absorbed through the skin. Acute oral and percutaneous toxicity tests in animals indicate that all three compounds exhibit little or no systemic toxic effects. Quaternium-18 Hectorite was also found to be nontoxic in an acute inhalation study. Subchronic oral and dermal toxicity tests on Quaternium-18 and Quaternium-18 Bentonite presented no evidence of systemic toxicity. No chronic studies have been reported.

All three Quaternium compounds under review here can be considered to cause at most only slight irritation to the animal skin. None has been reported to be skin sensitizing agents. In ocular irritation studies in rabbits, all three compounds have been shown to be at most mild irritants.

Clinical studies have determined that Quaternium-18 is practically nonirritating and nonsensitizing to the skin. Quaternium-18 Hectorite can be classified as a nonirritating, "nonfatiguing," and nonsensitizing agent; it does not present any adverse phototoxic or photoallergenic effects. Quaternium-18 Bentonite is not an irritating, "fatiguing," or sensitizing agent to the human skin. Quaternium-18 Hectorite exhibits no ocular irritation in humans.

There is no reported information concerning any of the Quaternium-18 compounds with respect to absorption, metabolism, storage, excretion, teratology, mutagenesis, or carcinogenesis.

CONCLUSION

On the basis of the available information presented in this report, the Expert Panel concludes that Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite are safe as cosmetic ingredients in the present practices of use and concentration.

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*Available upon request: Administrator, Cosmetic Ingredient Review, Suite 810, 1110 Vermont Ave., N.W., Washington, DC 20005

QUATERNIUM-18, QUATERNIUM-18 HECTORITE, AND QUATERNIUM-18 BENTONITE

A safety assessment of Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite was published in 1982 with the conclusion that these ingredients are "safe as cosmetic ingredients in the present practices of use and concentration" (Elder 1982). New studies, along with updated information below regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

Quaternium-18

Quaternium-18 is now reportedly used in hair sprays. The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition (Jensen and O'Brien 1993). The mean aerodynamic diameter of pump hair spray particles is $\geq 80\ \mu$, and the diameter of anhydrous hair spray particles is 60 to 80 μ. Typically less than 1% are below 10 μ, which is the upper limit for respirable particles (Bower 1999). Based on the particle size, Quaternium-18 would not be respirable in formulation.

Quaternium-18 was used in a total of 20 cosmetic products in 1976, with the largest single use in nail polish and enamel products at concentrations up to 1%. In 2001, Quaternium-18 was reportedly used in 90 cosmetic products (FDA 2001), with the largest single use in hair conditioners at a 2% concentration (CTFA 2001). Table 24 presents the available use information on Quaternium-18.

Quaternium-18 Bentonite

Quaternium-18 Bentonite was used in eight products in 1976, with the largest single use in other personal cleanliness preparations at concentrations up to 1%. In 2001, Quaternium-18 Bentonite was reportedly used in 221 products (FDA 2001), with the largest single use in lipsticks at concentrations up to 5% (CTFA 2001). Table 25 presents the available use information on Quaternium-18 Bentonite.

Quaternium-18 Hectorite

Quaternium-18 Hectorite was used in 142 products in 1976, with the largest single use in nail polish and enamel products at concentrations up to 5%. In 2001, Quaternium-18 Hectorite was used in 176 products (FDA 2001), with the largest single use in other personal cleanliness products at concentrations up to 19% (CTFA 2001). Table 26 presents the available use information on Quaternium-18 Hectorite.

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SQUALENE AND SQUALANE

A safety assessment of Squalene and Squalane was published in 1982 with the conclusion that these ingredients are "safe as cosmetic ingredients in the present practices of use and concentration" (Elder 1982). New studies, along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

Squalene

Squalene was used in 18 cosmetic products in 1976, with the largest use occuring in moisturizing preparations at concentrations of $\leq 10\%$. In 2001, Squalene was used in 29 products (FDA 2001), at a maximum use concentration of 10% in face powders (CTFA 2001). Table 27 presents the available use information for Squalene.

Squalane

Squalane was used in 400 products in 1976, with the largest use occuring in moisturizing preparations at concentrations of

[2]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

Current and historical frequency and concentration of use of Quaternium-18 and Quaternium-18 Bentonite

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Quaternium-18				**Quaternium-18 Bentonite**			
	2019[1]	**2001[2]**	**2018[3]**	**2001[2]**	**2019[1]**	**2001[2]**	**2018[3]**	**2001[2]**
Totals*	**61**	**90**	**0.46 – 0.95**	**0.1 - 2**	**199**	**221**	**0.15 – 2.5**	**0.8 - 9**
Duration of Use								
Leave-On	*18*	*27*	*0.46*	*0.1 – 2*	*199*	*218*	*0.15 – 2.5*	*0.8 - 9*
Rinse-Off	*43*	*63*	*0.76 – 0.95*	*1 – 2*	*NR*	*3*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	1	NR	NR	72	70	NR	4 - 9
Incidental Ingestion	2	NR	NR	0.7	108	138	NR	5
Incidental Inhalation-Spray	15[a]	1; 3[a]	0.46[a]	0.1 – 2[a]	3[a]; 1[c]	1[a]	2.5[a]	5[a]
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	0.29[b]	NR
Dermal Contact	1	16	NR	NR	86	79	0.29 - 1	0.8 - 6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	aerosol: 0.6	NR
Hair - Non-Coloring	58	68	0.46 – 0.95	0.1 – 2	3	NR	2.5	NR
Hair-Coloring	NR	1	NR	NR	NR	NR	NR	NR
Nail	NR	5	NR	NR	2	NR	0.15 – 0.25	NR
Mucous Membrane	2	1	NR	0.7	108	141	NR	5
Baby Products	NR	NR	NR	NR	NR	NR	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 these products are sprays, but it is not specified whether the reported uses are sprays.

[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.

[c] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, there fore the information is captured in both categories

NR – no reported use

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Concentration of Use by FDA Product Category – Quaternium-18 Compounds*

Quaternium-18 Quaternium-18 Hectorite
Quaternium-18 Bentonite Quaternium-18 Methosulfate

Ingredient	Product Category	Maximum Concentration of Use
Quaternium-18	Hair conditioners	0.76-0.95%
Quaternium-18	Tonics, dressings and other hair grooming aids	0.46%
Quaternium-18 Bentonite	Tonics, dressings and other hair grooming aids	2.5%
Quaternium-18 Bentonite	Foundations	1%
Quaternium-18 Bentonite	Basecoats and undercoats (manicuring preparations)	0.25%
Quaternium-18 Bentonite	Nail polish and enamel	0.15%
Quaternium-18 Bentonite	Deodorants Aerosol	 0.6%
Quaternium-18 Bentonite	Face and neck products Not spray	 0.29%
Quaternium-18 Hectorite	Lipstick	2%
Quaternium-18 Hectorite	Deodorants Aerosol	 3.2%

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

Information collected in 2018
Table prepared October 25, 2018