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

Status:	Draft Amended Report for Panel Review
Release Date:	May 15, 2020
Panel Meeting Date:	June 8 - 9, 2020

The Expert Panel for Cosmetic Ingredient Safety 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.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer, CIR.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Scientific Writer/Analyst, CIR
Date: May 15, 2020
Subject: Draft Amended Report on the Safety Assessment on Quaternium-18 and Quaternium-18 Bentonite

Enclosed is the draft amended report of the safety assessment of Quaternium-18 and Quaternium-18 Bentonite as used in cosmetics. (It is identified as *quater062020rep* in the pdf document.) The Expert Panel for Cosmetic Ingredient Safety (Panel) first reviewed the safety of these ingredients in 1982 and concluded that these ingredients are safe as used. In 2003, after considering new studies and updated use data on these ingredients, the Panel published the re-review summary in which it was stated that the Panel determined not to re-open the safety assessment. Because it was 15 years since the last review, the Panel re-reviewed Quaternium-18 and Quaternium-18 Bentonite at the September 2019 meeting, and determined to re-open the safety assessment to evaluate the sufficiency of inhalation data on Quaternium-18 Bentonite.

It should be noted that Quaternium-18 Hectorite was also included in the 1982 safety assessment and 2001 re-review. However, Quaternium-18 Hectorite is not included in the current assessment 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.

Summary data from the original 1982 report have been included in the draft amended report in *italicized text*. In addition, data that were included in the re-review document considered by the Panel at the September 2019 meeting have been included. A data supplement regarding an inhalation toxicity study on Quaternium-18 Bentonite was received (*quater062020data1*); please note, this information was previously included in the re-review document reviewed in September. Updated 2020 VCRP data were also received and included in this document (*quater062020fda*). No significant changes were noted from 2019 VCRP data.

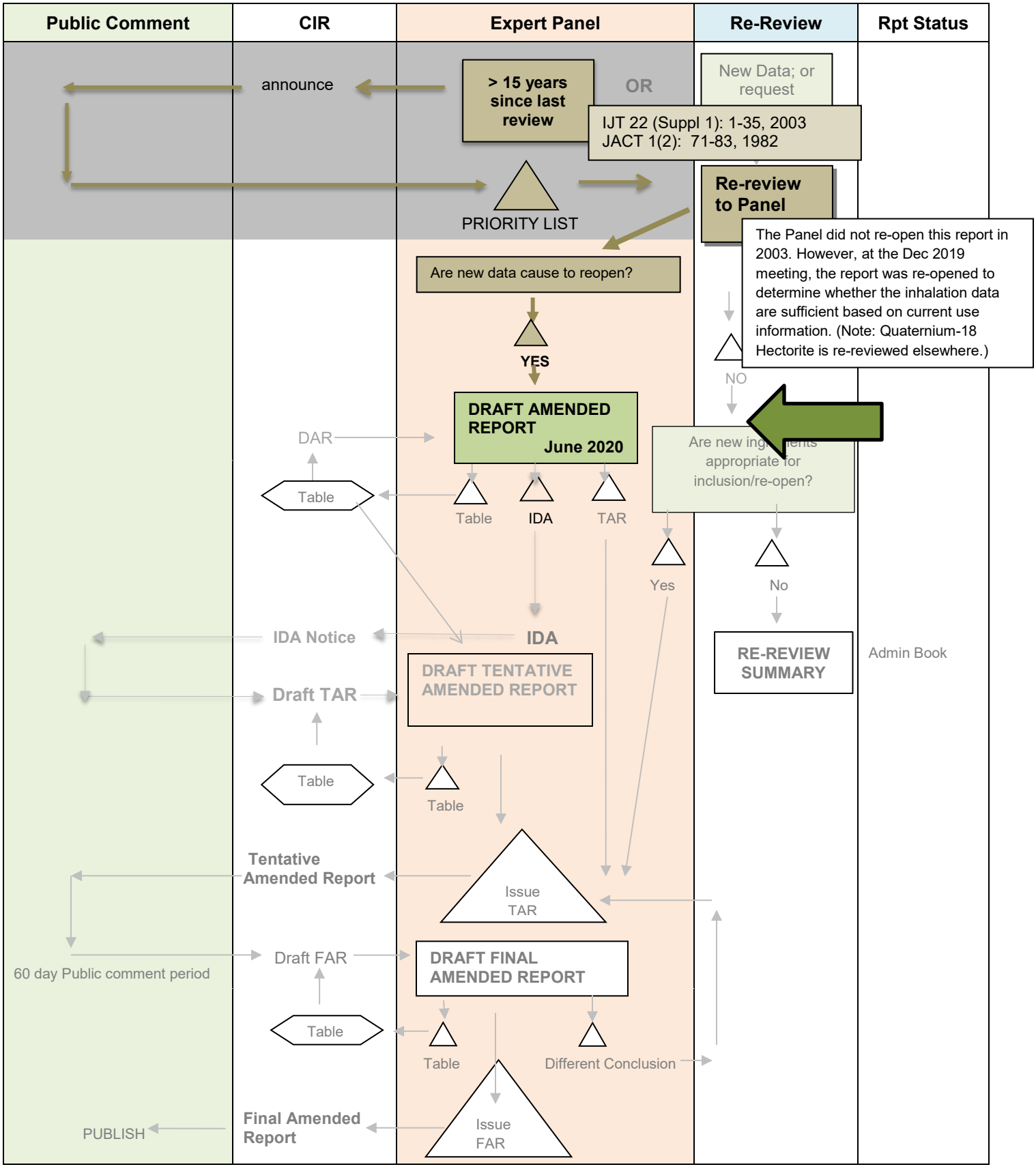
Summarized minutes from the initial re-review (November 2001) and full minutes from the September 2019 discussions have been included in this packet (*quater062020min*). Also included is the original 1982 safety assessment (*quater062020orig*), 2003 re-review summary (*quater062020RRsum*), report history (*quater062020 hist*), flow chart (*quater062020flow*), literature search strategy (*quater062020strat*), and data profile (*quater062020prof*).

The Panel should carefully consider and discuss the data (or lack thereof) presented in this report. If the Panel decides that no changes are necessary to the conclusion, the re-review may be closed. If a change is needed to the conclusion of this report, the Panel may issue a Tentative Amended Report with the appropriate conclusion. If data are insufficient, the Panel may issue an Insufficient Data Announcement (IDA).

RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Quaternium-18 and Quaternium-18 Bentonite

MEETING June 2020



*If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

Quaternium-18 and Quaternium-18 Bentonite Report History

1982

CIR published a safety assessment with the conclusion that Quaternium-18, Quaternium-18 Bentonite, and Quaternium-18 Hectorite are safe as used in the present practices of use and concentration as described in that report.

2003

The Expert Panel re-reviewed the safety of Quaternium-18, Quaternium-18 Bentonite, and Quaternium-18 Hectorite, and re-affirmed the original conclusion.

2013

Quaternium-18 Hectorite is reviewed in the Safety Assessment of Ammonium Hectorites as Used in Cosmetics. Quaternium-18 Hectorite was determined to be safe as used in the cosmetics in the present concentrations of use and concentration.

September 2019

The Expert Panel re-reviewed Quaternium-18 and Quaternium-18 Bentonite and determined to re-open the safety assessment due to insufficient inhalation data on Quaternium-18 Bentonite.

January 2020

2020 VCRP Data received

June 2020

The Expert Panel reviews the Draft Amended Report on the Safety Assessment of Quaternium-18 and Quaternium-18 Bentonite.

Quaternium-18 and Quaternium-18 Bentonite Data Profile – June 2020 – 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					XO			XO									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 – March 2020 -- 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)

NOVEMBER 2001 – RE-REVIEW MINUTES OVERVIEW

Full Panel

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 ReviewThe 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.

SEPTEMBER 2019 MEETING – RE-REVIEW

Belsito Team – September 16, 2019

DR. BELSITO: Quaternium-18. This is a re-review. The hectorite was included in the 1982 safety information and previous re-review, not included in the current one given issues that we won't discuss. It's been 15 years so we're looking at this.

The bentonite is here. Safety assessment of quaternium-18 and quaternium-18 bentonite. So, use down and concentration is down. Problematic given crystalline silica data. Need to reopen insufficient for inhalation for the bentonite. Or are we just dropping the bentonite -- why did we drop the hectorite and not the bentonite?

DR. HELDRETH: It got pulled into a different review.

DR. SNYDER: Re-review. Yeah.

DR. HELDRETH: Probably for inference or something to that effect.

DR. BELSITO: So the use for the quaternium-18 bentonite, I said it's not well defined. I looked at the old report and we don't have data to support in the old report for inhalation. So we would need to reopen because I don't think we have the data that says quaternium-18 bentonite is safe for aerosolized use.

DR. LIEBLER: Well, if it's being used.

MS. EISENMANN: Well, we don't know really if it's being used, it's just possible.

DR. LIEBLER: It's reported incidental inhalation.

MS. EISENMANN: Yeah, but those have -- it is possible that the products are sprayed. So, we don't know for sure that they're sprays.

DR. LIEBLER: Yeah. Well, if it's possible and we ignored it then we've got a problem. Think we have to reopen?

DR. BELSITO: Yeah.

DR. LIEBLER: Yeah.

DR. BELSITO: I mean, because if it's used in a product that can be aerosolized, we don't have the data to support a bentonite, right?

DR. LIEBLER: Right.

MS. EISENMANN: But you want to delay this report until you're actually working on the bentonite?

DR. BELSITO: I'd like to get rid of quaternium-18 bentonite and put it into the bentonites and just do quaternium-18. We got rid of the hectorite; why wouldn't we get rid of the bentonite? And then say quaternium-18 is safe as used.

DR. LIEBLER: I guess the issue is what's the driver here? Is it the bentonite or the --

DR. BELSITO: Quat-18 is used in a huge number of products.

DR. LIEBLER: Right.

DR. BELSITO: Because I have patients asking me all the time, quaternium-11, 22, and 18, do they cross-react with quaternium-15?

DR. LIEBLER: Well, if quaternium bentonite was not in here we would not reopen. Right?

DR. BELSITO: Right.

DR. LIEBLER: Yeah. So, we can just get rid of the bentonite and not reopen this. Put the bentonite in with the other silicates. Does it fit?

DR. BELSITO: I don't know, because we threw hectorite out of the report. Can we do that?

DR. HELDRETH: I mean, we've had other clays where we swapped out the cation, which is basically what this quat-18 is.

DR. LIEBLER: Right.

DR. HELDRETH: Maybe it could fit with those. The only issue is we're looking at a re-review clock. It's time to look at the safety in both of these ingredients again.

DR. BELSITO: Right.

DR. HELDRETH: Hectorite got out because it got picked up in 2013 for another reason. So, certainly you could say quaternium-18, safe as used, and move forward. But then we will have to bring the bentonite into something, or on its own or --

DR. LIEBLER: Well, I guess, how likely is it that we'll put together another silicates report in the near future, like this coming year?

DR. HELDRETH: As far as pulling it into a new report, there's no cation exchange clays on our priorities list right now.

DR. LIEBLER: Okay. So, this won't just fold in with the other clay silicates -- with the other silicates?

DR. HELDRETH: Right. Yeah. I mean, without sitting down and going and looking for frequency of use on cation exchange clays like this, my best guess is that they would get re-reviewed with the report that we did not that long ago.

DR. LIEBLER: Okay. So cation exchange clays are distinct from the other silicates that we decided to jet from the silica report this morning?

DR. HELDRETH: Some of those silicates could be that, but we specifically did a report on a handful of ingredients that were only cation exchange ones. Probably where it would fit best.

DR. LIEBLER: So what you're saying is that the quaternium-18 bentonite doesn't have a good place to land?

DR. HELDRETH: Timing-wise, yes.

DR. LIEBLER: Yeah. Timing-wise.

DR. HELDRETH: It's up for re-review right now.

DR. LIEBLER: Yeah. And what about the quaternium-18? Is there a better group it could go into?

DR. HELDRETH: Originally, quaternium-18, quaternium-18 bentonite, and quaternium-18 hectorite were all in one report. And that report is more than 15 years old. Hectorite got re-reviewed into a different report in 2013. It's got a new clock. So, both of these ingredients are left hanging out there needing a decision. Should we look at them again or no?

DR. BELSITO: So, we need to reopen because we don't have sufficient data to support quaternium-18 bentonite in a product that could be inhaled.

DR. LIEBLER: Let's just reopen it.

DR. BELSITO: And then we'll come in with the quaternium-18 as safe, and insufficient data for products that could be inhaled for the bentonite.

DR. HELDRETH: And then when we do the re-review of that exchanged cation group, then maybe we will pull the bentonite over.

DR. LIEBLER: Don't even mention that at this point. Bart, you're ahead. You're winning.

DR. HELDRETH: I'm trying to think of the whole timeline.

Marks Team – September 16, 2019

DR. SHANK: Do not reopen.

DR. MARKS: That's what I had too. Not reopen. So, Tom, we have your comments, not reopen. Ron Shank?

DR. SHANK: I agree.

DR. MARKS: Okay. Frequency and -- I'll go ahead and do a bit of a preamble on this or a post-amble, whatever. It was first reviewed, quaternium-18 and quaternium-18 bentonite, in 1982. Found to be safe in 2003.

It was reviewed again, and the decision was made to not reopen. The frequency and concentration of use has decreased. It appears that the three of us do not see any toxicologic alerts. The inhalation toxicity was addressed in the 2003 re-review; and I assume that's obviously still okay since we don't reopen. There was a silica impurity but the inhalation tests were fine.

For full disclosure, if one looked at the references, I do have a conflict of interest. There's a reference to quaternium-18 bentonite study to prevent poison ivy allergic contact dermatitis. In that study I was a consultant to the sponsor and the sponsor paid for that study to Penn State University. So, just for full disclosure. Ron and Tom, anything you want to add? I kind of summarized what my review was like.

DR. SHANK: I have nothing to add. I agree, do not reopen.

MS. SADRIEH: I just had a question. Quaternium-18 bentonite is in this and I think that you've removed the bentonite from the silica reports. I just was wondering if that's an issue or not.

MS. FIUME: Not to our knowledge, not with quaternium-18 bentonite. I believe there was safety data in the original review that were addressed.

DR. MARKS: Okay. Any other comments? If not, then tomorrow, I expect we'll second a motion not to reopen the review of these ingredients.

Full Panel – September 17, 2019

DR. BELSITO: Yes. So this is a re-review by virtue of the fact that we last looked at this in 1982. And, it's now problematic given the crystalline silica data. On the other hand, we have no place right now to put quaternium-18 bentonite, which is up for a 15-year review, in fact it's a little over; it's been 17 years.

So we felt that we had to reopen this report and that our conclusion would be that quaternium-18 is safe as used and the data is insufficient for quaternium-18 in bentonite in products that could be inhaled.

DR. BERGFELD: And that's your motion?

DR. BELSITO: That's our motion.

DR. BERGFELD: Is that a second or additional comment?

DR. MARKS: Yeah, we felt we didn't need to reopen it; we felt the inhalation tests were okay. There was an impurity with silica, but we felt the inhalation tests were okay. Ron, do you want to comment on that, frequency?

And I might mention here, I mentioned it yesterday. I have a conflict of interest. And particularly since quaternium-18 bentonite is the ingredient of question. I did a study, which is referenced in the paper, to prevent poison ivy and allergic contact dermatitis with quaternium-18 bentonite.

I was consultant to the company that made that product, and that company sponsored studies at Penn State. So just so you're aware of that. I don't know if -- Bart, I'll ask you, if you think that's too much of a conflict of interest for me to be the leader on our team for this ingredient let me know.

DR. HELDRETH: Yeah, I suppose just in the interest of being overly confident that we're not stepping across any conflict line, that maybe you would recuse yourself from the vote on that particular topic.

DR. MARKS: Will do. So, I will recluse myself on it from the vote. Do I need to recluse myself from still leading the team, or not?

DR. BERGFELD: I don't think so.

DR. MARKS: Okay.

DR. BERGFELD: Ron?

DR. SHANK: So, what was your motion, Don?

DR. BELSITO: That quaternium-18 is safe as used and quaternium-18 bentonite is insufficient for inhalation data.

DR. SHANK: Wasn't this a matter of opening the re-review or not?

DR. BELSITO: Opening it, right; and giving industry a heads up as to why we're reopening it; because we don't feel that the data support quaternium-18 bentonite in products that could be inhaled.

DR. SHANK: Okay. I didn't see the need to reopen it, but I'll go along with that.

DR. BERGFELD: So your motion, is it going to be seconded, to reopen it?

DR. SHANK: I'll second it.

DR. BERGFELD: Okay. Any other discussion?

DR. MARKS: I would think, as it's reopened, there should be lots of data for quaternium-18 bentonite since it is a rheologic ingredient used to thicken things like paints. And so I would think there would be quite a bit of additional inhalation data.

DR. BERGFELD: All right, any other comments? Seeing none, I raise the question -- you're not voting.

DR. MARKS: Oh, that's right. Thank you.

DR. BERGFELD: So, unanimous, with the exception of Dr. Marks who's recluse. All right, so it's going to be reopened, the quaternium-18. The next ingredient then is MCI/MI; Dr. Ron Shank is leading on that.

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INTRODUCTION

This is a safety assessment on Quaternium-18 and Quaternium-18 Bentonite as used in cosmetic formulations. The Expert Panel for Cosmetic Ingredient Safety (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.[1] In accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel evaluates the conclusions of previously-issued reports every 15 years. The Panel first considered a re-review of these ingredients in 2003; after considering new studies and updated use data on these ingredients, the Panel reaffirmed the existing conclusion.[2] In 2019, these ingredients were again considered for re-review, and the Panel decided to re-open the safety assessment to determine whether the new and existing data continue to support the safety of these ingredients in the present practices of use and concentration.

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 report because it was recently (2013) part of a separate assessment (Safety Assessment of Ammonium Hectorites as Used in Cosmetics).[3] In that 2013 assessment, Quaternium-18 Hectorite was determined to be safe as used in cosmetics in the present practices of use and concentration.

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*), Quaternium-18 is reported to function as an antistatic agent. Quaternium-18 Bentonite is reported to function as a dispersing agent – nonsurfactant.[4]

Quaternium-18 is a mixture of quaternary ammonium chloride salts, and Quaternium-18 Bentonite is the reaction product of Quaternium-18 with clays. Other alkonium clay-derived ingredients have been reviewed by the Panel and were considered to be safe as used. Data regarding these ingredients may be useful for inference purposes when evaluating the safety of Quaternium-18 Bentonite. The full report (Safety Assessment of Alkonium Clays as Used in Cosmetics)[5] can be found on the CIR website (https://www.cir-safety.org/).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the summaries of the previous report on Quaternium-18 and Quaternium-18 Bentonite are disseminated throughout the text of this document, as appropriate, and are identified by italicized text. (This information is not included in the summary section.)

CHEMISTRY

Definition and Structure

Quaternium-18 (CAS No. 61789-80-8) is the quaternary ammonium salt that conforms generally to the formula structure in Figure 1.[4] The hydrogenated tallow fatty radicals represented by "R" below, are derived from tallow fatty acids, the major constituents of which are oleic (37 - 43%), palmitic (24 - 32%), stearic (20 - 25%), myristic (3 - 6%), and linoleic (2 - 3%) acids.; minor components include cholesterol and arachidonic, elaidic, and vaccenic acids.[6] Quaternium-18 Bentonite (CAS No. 1340-69-8) is the cation exchange product of bentonite and Quaternium-18 and is depicted (with an example chain length) in Figure 2.

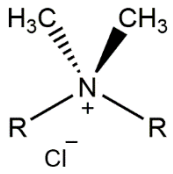

Figure 1. Quaternium-18 – wherein R represents hydrogenated tallow fatty radicals.

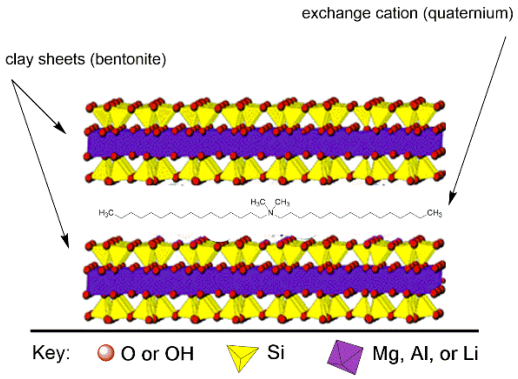

Figure 2. Quaternium-18 Bentonite

Physical and Chemical Properties

Quaternium-18 is a paste-like substance that is soluble in both water and isopropyl alcohol.[1] *Quaternium-18 Bentonite is a hydrophobic organo-clay compound that is expansible in water, methanol, ethanol, isopropanol, sorbitol, glycerin, and acetone.*

The median particle size of Quaternium-18 Bentonite is reported to be 28 µm.[5]

Method of Manufacture

No method of manufacture information was found in the published literature, and no unpublished data were submitted.

Impurities

Ditallow methylamine and sodium chloride are impurities associated with Quaternium-18 Bentonite.

According to a toxicity dossier, Quaternium-18 Bentonite contained an average amount of < 3% crystalline silica as an impurity.[7]

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

Based on 2020 VCRP data, Quaternium-18 Bentonite is reported to be used in 200 formulations, and Quaternium-18 is reported to be used in 70 formulations (Table 1).[8] Frequency of use has decreased for both of these ingredients since the initial re-review of this report, as Quaternium-18 Bentonite and Quaternium-18 were reported to be used in 221 and 90 formulations in 2001.[2] Concentration of use has also declined for both ingredients. The results of the 2018 concentration of use survey conducted by the Council indicate Quaternium-18 Bentonite is used at up to 1% in foundations and Quarternium-18 is reported to be used at up to 0.46% in tonics, dressings, and other hair grooming aids.[9] In 2001, the maximum concentration of use reported for Quaternium-18 Bentonite and Quaternium-18 was 9% and 2%, respectively, in leave-on products.

Quaternium-18 Bentonite is reported to be used in 72 formulations used near the eye (eyebrow pencil, eyeliner, eyeshadow, eye lotion, other eye makeup preparations); however, concentration of use data were not provided for formulations applied near the eyes.[8] These ingredients may result in incidental ingestion as Quaternium-18 Bentonite and Quaternium-18 are reported to be used in 108 and 2 lipstick formulations, respectively (concentration of use data were not provided).

Quaternium-18 Bentonite is used in aerosolized deodorant formulations (up to 0.6%) and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[10,11] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[12,13] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[13] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to

other cosmetic sprays. In addition, Quaternium-18 Bentonite is reported to be used in face powders, and could possibly be inhaled; concentration of use data were not reported for this uses. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[14-16]

Quaternium-18 and Quaternium-18 Bentonite are not restricted from use in any way under the rules governing cosmetic products in the European Union.[17]

Non-Cosmetic

Non-cosmetic uses of Quaternium-18 and Quaternium-18 Bentonite were not identified in the published literature.

TOXICOKINETIC STUDIES

Toxicokinetics studies were not found in the published literature, and unpublished data were not submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Quaternium-18

In an acute oral toxicity study, male rats received a test substance consisting of 5% Quaternium-18 and water via gavage in doses of 5 g/kg (n = 5) or 10 g/kg (n = 4).[1] An oral LD_{50} of 10 g/kg was established. In a different oral study, 6 rats/group were given up to 20 mL/kg of a 4% aqueous dispersion of Quaternium-18. The method of oral administration was not stated. The LD_{50} was reported to be > 20 mL/kg. An oral LD_{50} of 7000 mg/kg was determined in a study involving rats given a 75% aqueous suspension of Quaternium-18. No other details regarding this study were provided. Ninety-eight rats were orally administered up to 10 g/kg of a 70% solution of Quaternium-18 in isopropanol. The method of oral administration was not stated. The LD_{50} was reported to be 6.35 g/kg.

Fischer rats (5/sex) were given a single oral dose of 500 mg/kg Quaternium-18 and observed for 15 d.[18] Following dosing, the only sign of toxicity was generalized leg weakness, which cleared by day 2. The LD_{50} was > 500 mg/kg.

Quaternium-18 Bentonite

Quaternium-18 in cottonseed oil was given to 20 rats in doses of 8 g/kg.[1] An LD_{50} of 8 g/kg was established.

Inhalation

Quaternium-18 Bentonite

Five male and five female Sprague-Dawley rats were exposed to Quaternium-18 Bentonite for 262 min in a stainless steel and glass chamber.[7] 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 µm, with 30% of collected particles ≤ 10 µm in size. Animals were observed for 14 d following exposure. No mortality or irreversible signs of toxicity were seen in any animal after the exposure.

Short-Term Toxicity Studies

Quaternium-18

Varying doses of Quaternium-18 were fed to guinea pigs for 12 d.[1] The lowest dose level that produced signs of toxicity was 1 g/kg/d.

Quaternium-18 Bentonite

Groups of 12 weanling rats were fed diets containing up to 25% Quaternium-18 Bentonite for 12 weeks. No indication of toxicity was produced by the test substance.

Subchronic Toxicity Studies

Dermal

Quaternium-18 Bentonite

In a dermal toxicity study, 10 rabbits were depilated on their dorsa, and 0.5 g of Quaternium-18 Bentonite was applied under occlusion.[1] Applications occurred for 6 h/d for 90 d. No evidence of local or systemic toxicity of the test substance was found.

Oral

Quaternium-18

Dogs and rats were given 2800 ppm Quaternium-18 for 90 d. No signs of toxicity were observed. No other details regarding

this study were provided.

Chronic Toxicity Studies

Sprague-Dawley rats were given Quaternium-18 in the diet in amounts of either 0.2, 1, or 10 mg/kg/d for 6 mo.[19] Another group was given 500 mg/kg/d for 3 mo, and were killed on the last day of treatment. Group sizes ranged from 30-70 rats/sex. One group was left untreated and served as the control group. Animals in the high dose group displayed decreased body weight gain, decreased feed efficiency, and alterations in absolute and relative liver and kidney weights. An increase in incidence of adrenal cortical hydropic degeneration and enlarged mesenteric lymph nodes was also noted in the high dose group. There were no significant findings in macroscopic or microscopic observations for animals treated with 10 mg/kg/d or less.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

No developmental and reproductive toxicity studies were found in the literature, and unpublished data were not submitted.

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.[7] The test substance, Quaternium-18 Bentonite, was used at concentrations of 10, 30, 100, 300, and 3000 µg/plate. The test substance was considered to be non-genotoxic. No toxicity was observed in an Ames assay using *S. typhimurium* TA 100 at up to 5000 µg/plate.

CARCINOGENICITY STUDIES

No carcinogenicity studies were found in the literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION

Irritation

Quaternium-18

An aqueous dispersion containing 5% Quaternium-18 (0.5 mL) was applied to an intact and abraded area of the skin of 6 rabbits.[1] Applications were covered by a gauze patch for 24 h. No irritation was observed. A similar study performed with a 4% dispersion resulted in comparable observations (species not specified). A Draize assay was performed using a test substance containing 75% Quaternium-18 (species not specified). The primary irritation index (PII) was calculated to be 1.92 out of 8. In a different study, a 75% aqueous dispersion of Quaternium-18 was evaluated for skin irritation in rabbits. Patches containing 0.05 g of the test substance at concentrations of 2, 5, and 10% were applied to the skin and removed after 21 d. Mild irritation was noted at these concentrations.

Quaternium-18 Bentonite

Undiluted Quaternium-18 Bentonite (0.5 g) was applied to intact and abraded rabbit skin.[1] After contact was maintained for 6 h/d for 5 consecutive days, there were 10 days of rest and then 5 more days of exposure. No irritation was observed.

A test substance consisting of 5% Quaternium-18 Bentonite, 46% mineral oil, 45.8% water, 3% ethanol, and 0.2% parabens was tested for possible cutaneous irritation potential.[20] The test substance was applied daily to the skin of 3 rabbits (species not specified) for 6 weeks. The test substance was considered to be relatively well-tolerated.

Sensitization

Animal

Quaternium-18 Bentonite

The sensitization potential of Quaternium-18 Bentonite was evaluated in 12 guinea pigs.[1] An initial injection of 0.05 mL of the test substance (0.1% in physiological saline) was administered, followed by additional injections performed once per week for 3 weeks. After a 2-week rest period, a challenge dose of 0.05 mL was injected. No signs of sensitization were observed.

Human

Quaternium-18

A repeated insult, occluded patch test was performed on subjects (25/sex) using a test substance containing 7.5% Quaternium-18 (unspecified diluent).[1] The PII was calculated to be 0.26/8 and the mean skin sensitization index was 0.08/8. The test substance was considered to be non-irritating and non-sensitizing.

Quaternium-18 Bentonite

A repeated insult patch test was performed in order to evaluate the sensitization potential of two eyebrow color preparations (4.1 or 4% Quaternium-18 Bentonite) on 50 subjects.[1] No signs of irritation or sensitization were observed.

OCULAR IRRITATION STUDIES

Quaternium-18

One tenth of a mL of a 5% aqueous dispersion of Quaternium-18 was placed in one eye of 6 rabbits.[1] No irritation was observed during the 72-h observation period. Similarly, no irritation was observed when the same procedure was performed using a 4% dispersion of Quaternium-18. An eye irritation assay was performed in rabbits using a 75% suspension of Quaternium-18. The test substance (0.1 mL) was diluted to 10% and instilled into the conjunctival sac. The eye irritation score was reported to be 11.7/110 (minimally irritating).

Quaternium-18 Bentonite

A 10% suspension of Quaternium-18 Bentonite in physiological saline was placed in the eyes of 10 rabbits.[1] No signs or irritation were noted during the 24-h observation period.

A test substance consisting of 5% Quaternium-18 Bentonite, 46% mineral oil, 45.8% water, 3% ethanol, and 0.2% parabens was tested for possible ocular irritation potential in rabbits.[20] No details regarding this study were provided. Readings occurred 1 h, 24 h, 2 d, 3 d, 4 d, and 7 d after administration. The acute ocular irritation index was reported to be 11.33/100.

MUCOUS MEMBRANE IRRITATION STUDIES

Quaternium-18

The mucosal irritation potential of a 75% aqueous dispersion of Quaternium-18 was evaluated in rabbits.[1] The test substance, at a concentration of 10%, was applied in an amount of 0.2 mL to penile mucosa. Grading of the irritation gave a score of 0.43/4.

SUMMARY

In 1982, the Panel published a safety assessment with the conclusion that Quaternium-18 and Quaternium-18 Bentonite were safe as used. In 2003, these ingredients were re-reviewed and the original conclusion was re-affirmed. In 2019, these ingredients were again reviewed, and the Panel decided to reopen the safety assessment due to lack of inhalation toxicity data on Quaternium-18 Bentonite.

Quaternium-18 is a mixture of quaternary ammonium salts and Quaternium-18 Bentonite is the reaction product of Quaternium-18 and bentonite clays. Quaternium-18 and Quaternium-18 Bentonite are reported to be used as an antistatic and dispersing agent – non-surfactant, respectively.

Since the initial re-review was considered, frequency and concentration of use have decreased for both ingredients. According to 2001 VCRP data, Quaternium-18 and Quaternium-18 Bentonite were used in 90 and 221 total formulations, respectively. In 2020, VCRP data indicate that Quaternium-18 is used in 70 formulations, and Quaternium-18 Bentonite is used in 200 formulations. In 2001, the maximum concentration of use for Quaternium-18 Bentonite was reported to be 9% in leave-on products, while in 2018, the maximum concentration of use was reported to be 2.5% in leave-on products. 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.

The oral LD_{50} for Quaternium-18 in Fischer rats (5/sex) was reported to be > 500 mg/kg. An acute inhalation study was performed on Sprague-Dawley rats (5/sex). Rats were exposed to Quaternium-18 Bentonite for 262 min and 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 262 min exposure.

Sprague-Dawley rats were given Quaternium-18 in the diet in amounts of up to 10 mg/kg/d for 6 mo. Another group was given 500 mg/kg/d for 3 mo. Adverse effects were reported in animals dosed with 500 mg/kg/d, there were no significant findings in macroscopic or microscopic observations for animals treated with 10 mg/kg/d or less.

No genotoxicity was observed in Ames assays performed on *S. typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 at up to 3000 µg/plate. Similarly, no genotoxicity was observed in an Ames assay performed on *S. typhimurium* TA 100 at up to 5000 µg/plate.

A test substance consisting of 5% Quaternium-18 Bentonite, 46% mineral oil, 45.8% water, 3% ethanol, and 0.2% parabens was considered to be relatively-well tolerated when tested repetitively on the skin of 3 rabbits. The same test substance was used in an ocular irritation assay. The acute ocular irritation index was reported to be 11.33/100.

DISCUSSION

To be formulated.

CONCLUSION

To be determined.

TABLES

Table 1. 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**			
	2020[8]	**2001[2]**	**2018[9]**	**2001[2]**	**2020[8]**	**2001[2]**	**2018[9]**	**2001[2]**
Totals*	**70**	**90**	**0.46 – 0.95**	**0.1 - 2**	**200**	**221**	**0.15 – 2.5**	**0.8 - 9**
Duration of Use								
Leave-On	*18*	*27*	*0.46*	*0.1 – 2*	*200*	*218*	*0.15 – 2.5*	*0.8 - 9*
Rinse-Off	*53*	*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	2	NR	0.29[b]	NR
Dermal Contact	1	16	NR	NR	87	79	0.29 - 1	0.8 – 6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	0.6[d]	NR
Hair - Non-Coloring	66	68	0.46 – 0.95	0.1 – 2	3	NR	2.5	NR
Hair-Coloring	1	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

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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.

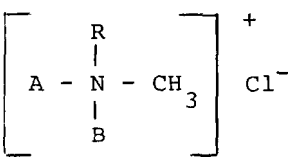
These compounds are only slightly irritating to the animal skin, and are not sensitizing agents. In ocular irritation studies all three compounds have been shown to be at most mild irritants.

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.

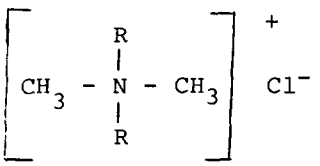
CHEMICAL PROPERTIES

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

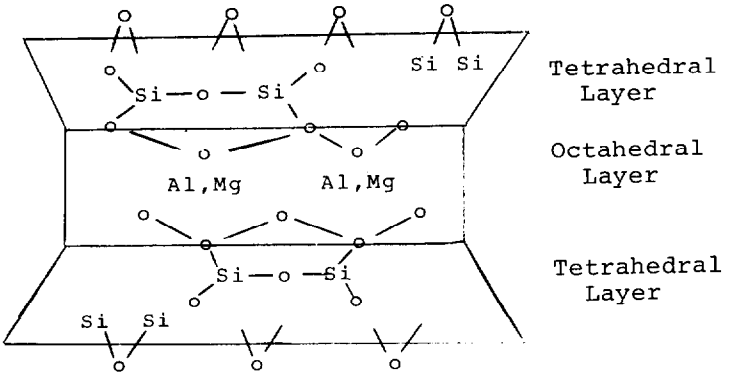
Quaternium-18: As a result of its polar nature, Quaternium-18 exhibits hydrophilic properties. A paste-like substance, it is soluble in both water and isopropyl alcohol.[2]

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

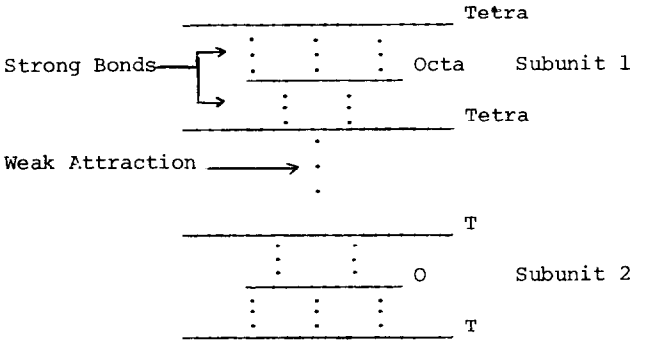
disturbed, it tends to become more fluid, which adds aesthetic value to certain cosmetic products.[5,6]

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

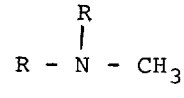
Four techniques are described for the determination of quaternary ammonium chloride salts.[2]

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

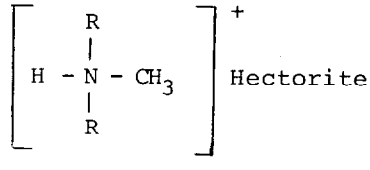
Three groups of impurities are associated with Quaternium-18 Hectorite and Bentonite. These are listed below in descending order of predominance (concentrations not reported).[2]

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.

Quaternium-18 and Quaternium-18 Bentonite 2020 Frequency of Use

Quaternium-18

Hair Conditioner	47
Rinses (non-coloring)	5
Tonics, Dressings, and Other Hair Grooming Aids	14
Other Hair Coloring Preparation	1
Lipstick	2
Moisturizing	1

Quaternium-18 Bentonite

Eyebrow Pencil	9
Eyeliner	42
Eye Shadow	14
Eye Lotion	1
Other Eye Makeup Preparations	6
Tonics, Dressings, and Other Hair Grooming Aids	3
Face Powders	2
Foundations	4
Lipstick	108
Makeup Bases	2
Other Makeup Preparations	5
Nail Polish and Enamel	2
Face and Neck (exc shave)	1
Other Skin Care Preps	1

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: November 1, 2019

SUBJECT: Quaternium-18 Bentonite

Anonymous. 2019. Summary of an acute inhalation study of Quaternium-18 Bentonite.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

November 2019

Summary of an Acute Inhalation Study of Quaternium-18 Bentonite

INCI Name: Quaternium-18 Bentonite

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 ≤ 10 um in size. Average chamber temperature was 21 °C. Average chamber relative humidity was 51%.