GREEN BOOK 1

Trimoniums

CIR EXPERT PANEL MEETING
JUNE 28-29, 2010

Cosmetic Ingredient Review
Commitment . . . Credibility
Since 1976

June 29, 2010

MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.

Scientific Analyst and Writer

Subject: Draft Amended Report for Trimoniums

At the April, 2010 Panel Meeting, the trimoniums re-review was re-opened add ingredients to the assessment. Attached is the resulting Draft Amended Report. Comments from industry were received and addressed.

Trimonium ingredients were divided into five chemical groups: 1) straight and branched chain alkyl trimonium (and their salts); 2) amide trimoniums (and their salts); 3) alkanol trimoniums (and related ethers/esters/acids); 4) glycol trimoniums (and related ethers /esters); and 4) polymers containing trimoniums. At the April meeting, the Panel members considered the groupings. The Panel asked CIR to review safety data on the ingredients and prepare a draft report. The Draft Amended Report includes all available data on these ingredients.

The history of the progress of this safety assessment, the search strategy, and transcripts from the last meeting are attached.

The Panel discussion will form the basis for the new discussion section in the report that will explain how and why the data in the original safety assessment is relevant to the expanded ingredient scope and address any particular issues with individual ingredients. We recognize that this is a significant expansion and the Panel should use this opportunity to confirm that is tis appropriate.

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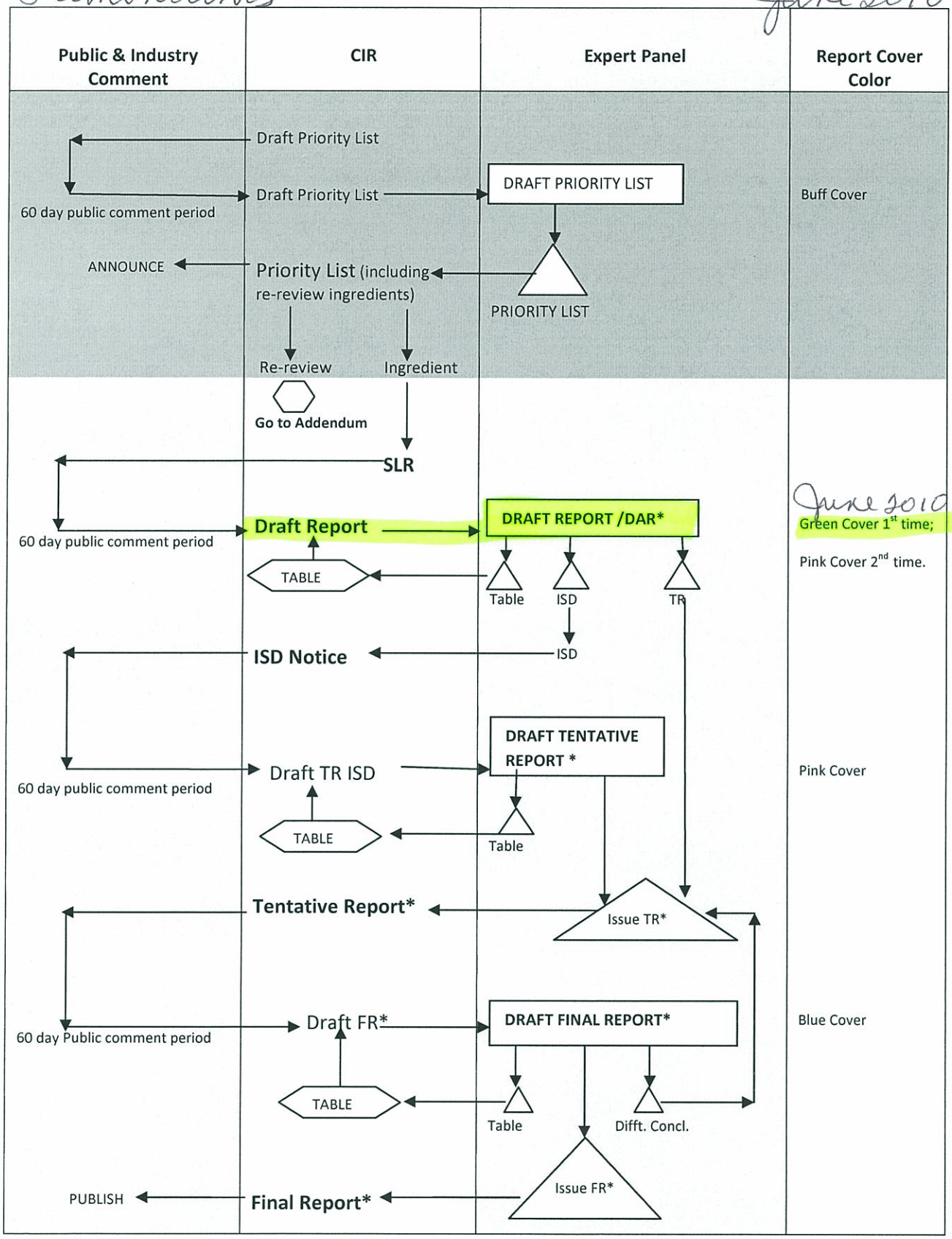
SAFETY ASSESSMENT FLOW CHART

Trimonicums

June 2010



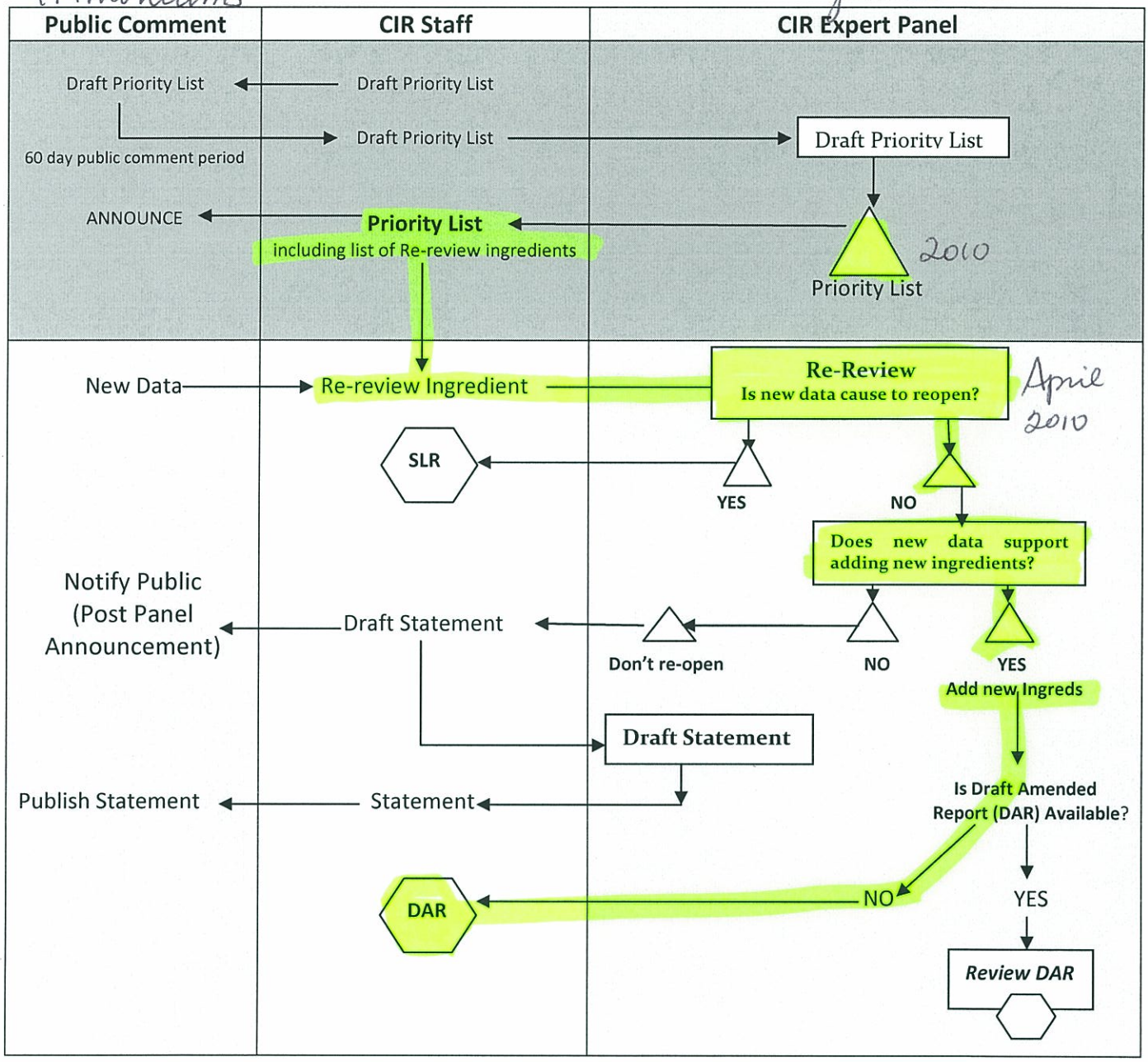
* For ingredient groups originating as Re-Reviews, add word "Amended" before Report; (DAR: Draft Amended Report).

△ Expert Panel Decision

▭ Document for Panel Review

SAFETY ASSESMENT FLOW CHART: RE-REVIEW ADDENDUM

Trimoniums June 2010



CIR Expert Panel Decision Points

Document for Panel Review

Go To Safety Assessment Flow Chart

History of Trimoniums

1997 - A safety assessment of cetrimonium chloride, cetrimonium bromide and steartrimonium chloride was published in 1997.[1] These cosmetic ingredients were found to be "…safe for use in rinse-off products and …safe for use at concentrations of up to 0.25% in leave-on products."

2009 – Behentrimonium chloride put on CIR priority list. Above ingredient due for a re-review soon so the re-review and the new ingredient were combined.

April 2010 – Panel confirmed conclusion from original safety assessment. Panel reopened to add behentrimonium chloride and several other groups of ingredients:. However, there was disagreement as to which of the groups (straight and branched alkyl chained trimoniums, amide trimoniums, alkanol trimoniums, glycol trimoniums, and polymers containing trimoniums) should be added. So the final decision for the add-ons was tabled until the draft tentative amended report could be written. The Panel rejected the saccharinate and trichlorphenoxide salts.

Search Strategy for TRIMONIUMS

PUBMED

Trimonium, *trimonium*, *trimonium, trimonium*

Only 2 results

Ceteartrimonium

No results

Cetrimonium (1995 -)

855 results

TOXNET

112-02-7 [cetrimonium chloride]

70 results, 17 possibly useful

17301-53-0 [behentrimonium chloride]

No results

Ceteartrimonium Chloride [no CAS No.]

No results

57-09-0 [cetrimonium bromide]

280 results, 43 possibly useful

DOGPILE.COM

Entered each of the available CAS Nos. and searched the first 2 pages of results.

No articles. A few MSDSs. One very good fact sheet with references to check out.

Results were culled by the toxicologist for relevance.

Search Strategy after Reopening and Additions

PUBMED

Entering CAS Nos and names of add-ons – ordered a total of 487, almost all for carnitine and choline.

EPA HPV Website

Checked CAS Nos. against list.

P R O C E E D I N G S

(9:10 a.m.)

DR. BELSITO: Okay. So we'll start the team meetings. And the first one is the trimoniums. And this was all driven by the fact that behentrimonium chloride was supposed to be reviewed this year and then, of course, according to our new procedures we looked at how we could group this with any other chemicals that were in the dictionary. And it turned out that among the many chemicals that we could possibly group them with were three that we previously reviewed in 1997. That was cetrimonium chloride, cetrimonium bromide, and steartrimonium chloride. So they decided to take those back into the fold since they would be due for re-review in a couple of years and then make this full list.

So I guess before we start looking at all of the data -- because I think the biggest issue is going to be the irritation of these chemicals and we can probably end up saying safe as used when formulated not to be irritating. The

question is what is safe as used? Where are the groups? And where are we going to make these cut offs? So I don't have a clue. And I'll turn it over to Dan and Bart maybe to comment on the groupings.

DR. LIEBLER: Okay. Well, I actually felt that most of the compounds in this group are reasonable to include and group together except for the polymers, which are really chemically distinct. They actually have different uses and very different properties. So there are some chemical similarities, but not enough that they really belong with the rest of the trimoniums. That's it in a nutshell for me.

DR. BELSITO: So that would be -- going through the tables, I guess, of the potential add-ons, if we go back to Table 1 where the straight chain alkyl trimonium compounds and their salts. So you thought that all of those were okay for addition?

DR. LIEBLER: Right.

DR. BELSITO: Okay.

DR. LIEBLER: Table 5.

DR. BELSITO: I'm going through all the potential add-ons starting -- so there were none within that that gave you cause at all. And then Table 2 was the amide trimonium compounds and their salts. And you were pretty much okay with all of those.

Mark, do you have any comments so far?

DR. HELDRETH: No. I completely agree. It's just a matter of different chain length, different molecular size, but all the same types of functional groups.

DR. BELSITO: Okay. And then Table 3, the alkanol trimoniums. Again, the carnitine and the palmitoyl esters, all those you were okay with?

DR. HELDRETH: Right. Yeah.

DR. EISENMANN: One comment on that table. Choline chloride is not permitted for use in Europe. I don't know if you knew that or not.

DR. BELSITO: On Table 3.

SPEAKER: Yeah, very first one. Top of

page 36.

DR. EISENMANN: I think they're reconsidering that at this point, but it's not an (inaudible).

SPEAKER: Do you know why?

DR. BELSITO: It's more of a chemical prototype for this group anyway. I don't remember on the use on this.

DR. BRESLAWEC: It's also a dietary supplement.

DR. BELSITO: Yeah.

DR. LIEBLER: It's supposed to make you smarter.

DR. BELSITO: Choline chloride is not permitted in Europe.

DR. EISENMANN: In Europe at this point. They're reconsidering it as far as I know because (inaudible) at this point. It got put on originally so there's no reason as to why. I think there is dermal penetration data on it. It's not well absorbed, so, I mean, there was some data (inaudible).

DR. BELSITO: But Halyna just said it's a dietary supplement.

DR. BRESLAWEC: It is. I think that's an area that we'll have to explore further before being comfortable -- where you would be comfortable (inaudible) on this particular ingredient, yes.

DR. BELSITO: Okay. And then Table 4 is the glycol trimonium compounds and related ethers and esters. And again you're okay with that?

DR. LIEBLER: Right.

DR. BELSITO: Okay. And then Table 5, the polymers were a definite no. Okay. So then having that as sort of a general background I guess we come back to the question Wilma addressed because some of these are ethers and esters. The original goals was just to do esters and salts, but you're okay with the addition of ethers?

DR. LIEBLER: Yeah.

DR. BELSITO: And for the non-chemists among us, those are going to be broken down.

DR. BRESLAWEC: You may want to explain

how we grouped them and what the rationale was behind not including it.

DR. HELDRETH: In contrast to the esters, which we know are often (inaudible) esterases break down to the alcohol and the acid, ethers are a lot more durable. They're harder to break down. They're very similar in their stability to simple alkanes. And so it's less likely to metabolize into something else.

DR. BELSITO: So it's likely just to stay put as it was put into the skin and either get absorbed or not get absorbed. If it gets absorbed then it gets metabolized internally in the body? No?

DR. HELDRETH: To an extent, but it's more durable.

DR. BELSITO: Still more durable.

DR. HELDRETH: Unlike an esterase which is going to cleave these esters really quickly. The ethers -- there's not really etherases.

DR. LIEBLER: I mean, ethers are cleaved -- oxidated, I believe, by cytochrome P450s.

DR. BELSITO: Okay.

DR. LIEBLER: There is some of that activity in the skin, but you have to penetrate the stratum corneum to get to that activity. The esters are much more cleavable by a broader range of esterases in the epidermis.

DR. BELSITO: Mm-hmm. Okay. So at least conceptually so far what I'm hearing is the groups in Table 1 to Table 4 are conceptually okay; Table 5 not.

DR. LIEBLER: Right. I mean, I think the dominant feature of all those groups in Tables 1 through 4 is the quaternary ammonium nucleus. And the side chains simply, you know, whether they have amides or ether link because they are straight chain alkanes are simply more or less polar substituents of that basic structure.

DR. BELSITO: Okay. Then I think the next question is within those groups are there certain chemicals that we're concerned about? So, for instance, in Table 1, which I thought was somewhat of a no-brainer, we have laurtrimonium

trichlorophenoxide. I know nothing about trichlorophenoxide. And I don't know that we've ever reviewed anything that comes to trichlorophenoxide. And that trichlorophenoxide molecule looks pretty active to me.

DR. LIEBLER: Yeah. I was surprised to see that as the salt that's listed uses cosmetic biocide. And I'm not sure what -- whether the trichlorophenoxide part is -- anion is supposed to have any bio activity at all. I did notice -- I think there were a couple of compounds that had that. Or maybe that's just the one. But that certainly bears more scrutiny whereas the other chlorides and bromides and sulphants are not much of an issue.

DR. BELSITO: Because I had a lot of questions within some groupings of chemicals. Maybe we can go down the ones I had questions on since I'm probably the most naïve person here in this regard and then -- so the first I thought that we might want to bounce out is the trichlorophenoxide in that group. I don't know.

Do people (inaudible) to be kept in or?

DR. SNYDER: I'm just totally -- I mean, I'm out of my league, too, as far as getting a little bit --

DR. LIEBLER: I recognize the species as, you know, a halogenated phenol basically. And I was surprised to see it there, but I don't really have any reason to suspect that it would have any adverse effect. But I honestly don't -- I'm not familiar with this stuff. I wouldn't necessarily think it's terribly reactive. It probably wouldn't be in a product like this or an ingredient like this if it were, but I don't think it's going to be chemically unstable for that matter. But it would probably require us to have much more scrutiny of that piece than any of the other more simple salts -- simple anions.

DR. BRESLAWEC: I think we may want to see how often it's used, if at all.

DR. BELSITO: And then the cetrimonium methosulfate. We're okay -- I mean, have we --

DR. LIEBLER: I don't have any reason to

be concerned about methosulfate.

DR. BELSITO: Okay.

DR. LIEBLER: It's pretty similar. It's pretty simple.

DR. BELSITO: And the -- have we -- we have not done -- I mean, I know this is getting silly, but just to look at -- the other team has sometimes reacted and specifically thinking about rice, we haven't done saccharinic acid, have we? So I just question that.

DR. LIEBLER: Right. Same. I feel the same way about the saccharin and the tosylate as I do about the trichlorophenoxide.

DR. BELSITO: So --

DR. LIEBLER: So does the cetrimonium tosylate right below the saccharinate.

DR. BELSITO: That was with my next one.

DR. LIEBLER: Yeah. Those are basically just unknowns in my view.

DR. BRESLAWEC: Okay. So what you're suggesting is to throw out the saccharinates and tosylates?

DR. BELSITO: Yeah. And the trichlorophenoxides.

DR. BAILEY: Is the saccharinate related to saccharin itself? Is it saccharin?

DR. EISENMANN: I think so, yes.

DR. BAILEY: Okay. So it's already a food additive. It's an artificial sweetener.

DR. EISENMANN: I don't know that it's used (inaudible).

DR. BELSITO: Yeah, but if you remember the rice data --

DR. BAILEY: I do remember it.

DR. BELSITO: There were conversations where what you put on the skin and what gets ingested could be very different. Just pointing things out. Just trying to be proactive here.

SPEAKER: So that would apply to all the saccharinates?

DR. BAILEY: I think so. I mean, we have to hear what the other group says about it.

DR. BRESLAWEC: As you may have noted, in this particular group we tried to be as

exhaustive as possible to group them logically to allow the panel to kind of -- to express its reasoning for including or excluding certain types of additives which would give us guidance. So this is (inaudible).

DR. BELSITO: Okay. So the methyl sulfates we're going to be okay with. Ethers we're okay with.

SPEAKER: Right.

DR. BELSITO: Okay. Okay.

DR. BRESLAWEC: There are no uses for laurtrimonium trichlorophenoxide, cetrimonium saccharinate, cetrimonium tosylate, and steartrimonium saccharinate.

DR. BELSITO: Okay. Well, let's get rid of them. Okay.

DR. LIEBLER: I think if you scroll down to Table 3 you have carnitine PCA. There's another interesting anion that I don't have any reason to be particularly concerned about, but it's just unusual. And I ask the same question about uses on that one.

DR. EISENMANN: I think there was a review for PCA.

DR. BRESLAWEC: No uses or concentrations (inaudible).

DR. BAILEY: Has PCA as an ingredient been reviewed? I don't have Internet connectivity here so I can't look it up.

DR. EISENMANN: I think so.

MS. FIUME: I think you're right. PCA and sodium PCA.

DR. EISENMANN: I think so.

DR. BAILEY: I think they've been reviewed.

DR. LIEBLER: So we might be all right with that.

DR. BELSITO: All right. So in Table 3 then the biggest question mark that we have is why choline chloride is not approved for use in Europe, but it is a food additive.

DR. EISENMANN: I mean, the opinions that are available, and they're still looking at irritation data, but there's data that need to be

included in the report I think.

DR. BELSITO: I mean, if it's irritation data, again, I think the way we're going to handle this is as we've done with all other irritants is to say safe and formulated, not to be irritating since we know that that depends upon what else you throw in there with the pHs, yadda, yadda, yadda. We really can't come up with those parameters in the conclusion. Okay.

DR. HELDRETH: If I may interject. If the choline chloride seems to be something that we later decide to remove, that may affect the esters because the choline chloride would be a metabolite of all these ingredients. So if it goes down, you may consider how it affects the esters that are in that same group in that same table.

For example, choline chloride would be an esterase metabolite of lauroyl ethyltrimonium methosulphate, or at least the chloride version.

DR. BELSITO: Right. I see what you're saying.

DR. BAILEY: Carol, do we know where

Europe is in their assessment?

DR. EISENMANN: I think they're waiting for more data and it's just irritation data. I don't think they know why they've put it on the list. The most recent opinion -- the industry has requested use of it to 5 percent and they don't have irritation data that high, so they're waiting for more irritation data. But there is dermal penetration data in the opinion, which would be nice to have.

DR. BELSITO: Yeah, to have in here.

DR. BRESLAWEC: It's pretty obvious we need to supplement with additional information, if available.

DR. BELSITO: And it's pretty obvious that the -- so the deal is it's not banned in Europe; it's just not approved for use.

DR. EISENMANN: No. It's on Annex 2. Right now it's not permitted for use in Europe, but we don't -- it was originally on the list, so we don't know why it was on the list.

DR. BAILEY: It's one of the old ones,

right?

DR. EISENMANN: Right.

DR. KATZ: Wasn't it that they didn't get the data that they asked for?

DR. EISENMANN: I don't know originally how they put things on the list.

DR. KATZ: Because that was basically you were on the list if -- when they call for data came through and you didn't provide the data within a period of time you ended up on the list.

DR. EISENMANN: So (inaudible) and now they're --

DR. BAILEY: Well, I mean, there are a lot of things on that early EU list that there's no documentation whatsoever. So I think you're probably right.

DR. KLAASSEN: Yeah. If they didn't get the data they put them there.

DR. BAILEY: So the data is now being provided it sounds like. So I think this argues to keep this in the group and then see what information we can get.

DR. BELSITO: Okay.
DR. LIEBLER: Yeah. I was looking to see uses on that and I can't find it. I'm looking up through Table 11 and I'm not, you know, I'm overlooking it.
DR. EISENMANN: I haven't done the concentration piece.
DR. LIEBLER: So we don't have that. Okay.
DR. BRESLAWEC: We have no uses or concentrations reported based on what we have for choline chloride.
SPEAKER: (inaudible)
DR. LIEBLER: That's right. I guess so.
DR. BELSITO: Okay.
DR. EISENMANN: I wanted to see if (inaudible) put it in the report.
DR. BELSITO: Okay. Well, let's keep it in at this point. And if, I mean, we should obviously in the next duration capture all the European data that they have. And if it comes down to the fact that we decide that all the data

that there is on it are safe and it's irritation that's missing, again, I think it's going to be the issue with every single one of these chemicals that we're looking at. And, okay. So.
And the glycol trimonium group. I guess there were none that we haven't in some way looked at. So basically we're going to throw out the saccharinates. We're going to throw out the -- there were just two, right?
DR. BAILEY: Trichlorophenoxide.
DR. BELSITO: Right, the trichlorophenoxide. But there were only two saccharinates, right?
DR. LIEBLER: Correct.
DR. BELSITO: Two of those and then we're going to throw out the tosylate. And there was just one of those.
DR. KLAASSEN: So why are we throwing out the saccharinate?
DR. BELSITO: Because we have no data on it.
MS. BECKER: If I get data do you want

it back in?
DR. BELSITO: Sure. But that's going to be a huge report, saccharin.
MS. BECKER: Yeah.
DR. BAILEY: Would that be excluded under CIR review rules, ma'am?
DR. BRESLAWEC: I think we have the option of excluding it under CIR Review. My guess is there's not a lot of dermal data on saccharin.
DR. EISENMANN: Since there's no uses reported?
DR. BRESLAWEC: But there are no uses reported so we might as well not keep it.
DR. BELSITO: Yeah. I would just toss it. It'll get us into a whole can of worms potentially.
DR. BAILEY: Good idea.
SPEAKER: Okay, so.
DR. LIEBLER: And I just have one other question. Is there a history for CIR on ricinoleic acid?
DR. BELSITO: Yes.

DR. LIEBLER: And its derivatives? Okay, good.
MS. BECKER: So trichlorophenoxide, saccharinate, and tosylate are out.
DR. BELSITO: And Table 5 is out.
MS. BECKER: And Table 5 is out. We're okay.
DR. BELSITO: Okay.
DR. SNYDER: On page 9 on the use, under the use paragraph, we really need to separate out, I think, leave-ons and rinse-offs because the old report had a limitation for leave-ons and we don't indicate that very clearly here. So I think we need to make sure that we make a distinction between the leave-ons and the rinse-off uses. We just say the survey of the current concentrations of use, I don't think we need that.
MS. BECKER: Okay.
DR. SNYDER: And that's only being driven because there was a limitation placed in a previous report which will probably follow through to this report.

MS. BECKER: Yes. Okey-dokey.
DR. BAILEY: Carol, you had also mentioned something about the guar hydroxypropyl trimonium chloride as one we want to add.
DR. BRESLAWEC: We had deliberately excluded the guar, that particular ingredient, Bart.
DR. HELDRETH: Yeah, the guar is essentially a gum. We're talking about a huge thing that would probably be thrown out just like the polymers are.
DR. EISENMANN: It's a high use ingredient so you would expect to see it in another report. Guar hydroxypropyltrimonium chloride.
DR. BELSITO: But there are a whole bunch of guar- based ingredients in cosmetics, right? I mean, it might be best to create a guar family. Have we looked at guar?
DR. EISENMANN: No. And there's a number of gums we haven't looked at.
DR. BELSITO: Right. And that alone is

a cosmetic ingredient.
DR. EISENMANN: There are a number of gums or polysaccharide trimonium chloride ingredients so I don't know at what point, but just a high use ingredient. I thought well maybe we should at least let you know that it's going to come up at some point.
DR. BELSITO: Yeah. But if we look at this and at some point we look at guar, then, you know, I think then those can all be added.
DR. EISENMANN: Okay.
DR. BELSITO: On page 15 under cetrimonium chloride -- two, four, six -- the ninth line down from the top it says, "There was intermittent and slight edema during week 4 in two rabbits." I'm assuming that's the number 4 or there was something missing. Seventeen. Right here.
MS. BECKER: I've got it. I left out which week?
DR. BELSITO: No, is it week 4 or the number 4 instead of F-O-R? Just check that. I

assumed it was week 4, but I didn't know if there was something missing from that sentence.
Under ocular irritation. And it says that in several in vivo studies, cetrimonium chloride is found to be irritating and caused, at least the studies in Table 15 it was reversible, not irreversible.
MS. BECKER: Okay. I'll double-check that.
DR. BELSITO: Yeah, and just -- it says Table 15, as low as.01 and irreversible. Yeah, because then it says in the eyes as rabbits as low as.01 and irreversible damage at 25 percent. In Table 15 I don't see any data at those concentrations. I just see three studies. So I'm just --
MS. BECKER: Got that.
DR. BELSITO: Okay. And then I guess this is just a general comment in reading these documents in cases like this where what's supplied is only 25 percent active. Or in cocamidopropyl betaine what's supplied is only 30 percent active.

I think particularly in terms of the sensitization irritation studies it would always be really nice for me if it would be put at the percentage of the actual compound we're looking at.
DR. BRESLAWEC: Of the active ingredient.
DR. BELSITO: Right. Of the active ingredient. Because then I have to keep doing the calculations of what was actually put on. And when we get to the CAPB document, I think sometimes there are questions as to, at least in my mind, what they were testing with. Was it X-percent active or was it X-percent of the 30 percent? And it's very hard to follow. So if we could just sort of make a general rule that it's translated to the percentage of active that was tested.
DR. SNYDER: I had the same problem on the CAPB.
DR. BELSITO: Yeah.
DR. SNYDER: It was very difficult to figure out exactly what that data meant.

DR. BELSITO: And so on page 17, I guess -- one, two, three, four -- from the fourth line from the bottom it says the low dose had Grade 1 erythema at 1-24-48. No edema was observed. The authors concluded that steartrimonium chloride was irritating to the skin at 20 percent," while, in fact, it was 4.08 percent because, I mean, that sentence gives the impression that the active at 20 percent was irritating, which it would be because the active at 4 percent was actually irritating. It was a dilution. And nonirritating at.408 percent.

DR. SNYDER: That makes sense.

DR. BELSITO: Yeah. So I think -- I know that they concluded that, but, you know, again they were doing 2 and 20 percent of a partial mixture. And it keeps happening on page 18. You'll see all the comments in my book.

SPEAKER: Okay.

DR. BELSITO: Those are the only comments I had on this report.

DR. LIEBER: I had a few. One comment

just on terminology in the first few pages of the report we refer to fatty acid chains. It's actually alkyl chains because there aren't fatty acids in these. Right? So there are a number of instances of that.

Also, on -- let's see. This would be page -- page where there's essentially a summary of a lot of short little bullet sentences or short paragraphs on the -- describing the composition and content or the chemical properties. It's -- that text is -- really, it's all stuff that's in the tables anyway. And what I think would be more useful to the reader would be sort of a more broad summary of the properties of the family of compounds that would help to orient the reader as to what they're dealing with.

For example, something like all of these compounds are waxy solids that are partially soluble in water and polar organic solvents. The most common contaminants are such and such and so and so. And in referring the readers to the tables for specific -- because otherwise it's just

really hard to follow.

And I have a similar comment later on in the report. Let's see. It would be page -- page 10. Again, on the reported uses it's just tough slogging. It might be possible to take sort of a higher level organizational view of the reported uses. This family is mainly used for such and such. This group is mainly used for so and so, as opposed to having a lot of individual sentences just about the individual compounds and what percents and numbers of products.

DR. BRESLAWEC: This may be a good point -- good time to mention that we're completely revamping how we're going to be presenting frequency use and concentration of use. We're going to have one review focusing on that and I think by June we will see a much smaller, more concise description of categories of use and then a splitting out of leave-on, rinse-off. And also address whether any special populations are affected. So there will be a lot less information, but it will have been analyzed and

presented in a way that I think it's easier to deal with.

DR. KLAASSEN: Great.

DR. SNYDER: So when we go to -- as we go to the current use and concentration tables -- so just go to page 53 and Table 11 -- so the table heading (inaudible) has a whole list of glycol trimonium ingredients. And so when we -- when I see that there's only one reported use in body as hand creams, lotions, powders, and sprays, which are a huge category, something under 44,.05 percent, does that mean that all of them are used in that? Or is that -- or just one of them used --

DR. BELSITO: That's a report from one company, right?

DR. BRESLAWEC: Yeah. That's a report from one company. Concentration use in that category of.05 percent.

DR. EISENMANN: Not necessarily.

DR. SNYDER: But what does that represent? See, for me I don't -- I'm really

struggling. But what does that represent because --

DR. EISENMANN: That represents the maximum concentration of use that was reported for that ingredient.

DR. SNYDER: Those ingredients. Because --

DR. EISENMANN: No, for that one.

DR. BELSITO: No, dihydroxypropyltrimonium chloride.

DR. BRESLAWEC: Even though FDA did not report --

DR. BELSITO: No, just the tridihydro.

DR. SNYDER: Oh, okay.

DR. BELSITO: Lauroyl we have one FDA report with no concentration of use.

DR. SNYDER: So for me it seems like we've kind of gone 180 degrees in the other direction where we used to have a few ingredients that had no reported uses and then we captured that by saying in the present practices of use. But I think we're getting such a large group now

of ingredients with absolutely no reported uses or we don't know the concentrate. We have data gaps with a large grouping. And I'm becoming uncomfortable.

DR. BELSITO: But have you done an exhaustive company check at this point, Carol, on this family, or?

DR. EISENMANN: I know I haven't done the carotene and the choline chloride and that group. There might be some gaps here and there in some of the other ones because the original list was different from this list. So I thought I'd wait until you actually decided what ingredients you're going to include in the reports.

DR. SNYDER: So for me the biocide issue is easily resolved because that's usually a very, very low percentage that's added, so you have some competence in that if it's used in the biocide it's probably not as significant -- represents not a significant exposure.

DR. EISENMANN: Right.

DR. SNYDER: But then there's these

other things that creep up where it's up to 10 percent. And then -- so then I'm saying are we inferring by our conclusion that we're saying that somebody could use that up to 10 percent?

DR. EISENMANN: I don't know that you ever have a percent in there. Again, unfortunately, I have to try to be careful about asking about the active because they might be telling me they're putting in as they get it from the supplier.

DR. SNYDER: Tell in Table 10 we do have 10 percent.

DR. EISENMANN: Which table?

DR. SNYDER: On Table 8. I'm sorry. Table 8 there's a category 1226 goes up to 10 percent. And then there's 7 percent and -- so then that starts -- that's not just.17 percent or.017 percent. So I'm just --

DR. BELSITO: But again, I think Carol made a good point. She needs to be very specific with the companies when she's asking is the percent they're giving active or is the percent

they're giving what they dilute and what they receive from the manufacturer, which is, you know, 20 percent or whatever. So I think we need to start, you know, whenever we see an ingredient that's not supplied at 100 percent, that just has to send up a red flag that everyone dealing with it has to be dealing with active and not just what are you doing with this.

DR. EISENMANN: Right.

DR. LIEBLER: I would also like to say on Figure 1, the representation of the structures, I would say I like the general idea of what you're trying to do, but you've managed to come close to representing these molecules in their actual size. Which is, you know, sort of atomic force microscopy would allow you to see these.

I think -- I would suggest that you use perhaps one or two of the examples of the family of increasing chain length as an example figure and then incorporate the rest of the information in a table where you can summarize the structures more efficiently because this just -- it's a nice

idea, but it's unreadable. Maybe take another run at this idea of how to illustrate the structure of relationships. It's a good basic idea, but it just didn't work here because of the very small size of the structures you had to represent. It's just unreadable.

SPEAKER: True.

DR. HELDRETH: So maybe something like a spreadsheet where it would positionally lay down different structure points?

DR. LIEBLER: Yeah, you could do that. I mean, you know, Figure 1A is a nice -- or 1C, excuse me, is a nice map that shows the choline derivatives and how the alkyl chains attach and how the family develops. But you might have one or two maps like that, but use the space more efficiently somehow. I think in a way you're constrained by the size of the font you're using for the typeface as opposed to the structures. Maybe let the structures dictate the sizing instead of the typeface.

DR. HELDRETH: Sure. Thank you.

DR. BELSITO: Any other comments? I guess the one thing -- because there wasn't a heading -- that is clearly missing is we have no method of manufacturing and impurities for any of these. And are we going to be able to get it? We've got this -- I don't know (inaudible) because what we were looking at was trying to figure out how to group families or --

DR. BRESLAWEC: That was the objective. We were trying a little different approach. See if we can get some guidance from the panel early on before we spend a lot of time generating a lot of data that may or may not be useful. So, yes, we (inaudible).

DR. BELSITO: And, you know, that's fine, I think, you know. But maybe when we're doing these a little heads up. You know, this is a very preliminary report to try and gather information on where the panel is going into developing a family and the information we're going to include is primarily to help guide to develop this family.

MR. SILBERGELD: Are you about to leave this report?

DR. BELSITO: We're asking for all comments, so --

MR. SILBERGELD: Rachel had a -- from Table 7 -- a list of what she identified as new ingredients: Cetrimonium bromide in lips -- or new uses anyway; cetrimonium bromide in lipsticks and aftershaves; cetrimonium bromide in baby products, fragrances, and deodorants; and behentrimonium chloride in baby shampoos. She believes those are new uses and wants to know does that raise any questions -- any new questions.

DR. BELSITO: Some of the reason why it may be a new use has to do with how products were grouped when this was originally looked at. Is that not correct?

MS. BECKER: Yes.

DR. BELSITO: I can never keep track of how things were grouped back in the early '90s versus -- baby products did have a grouping then, right?

MS. BECKER: Yes.

DR. BELSITO: And lips --

MS. BECKER: The only thing that's really changed since the original one was -- I think this was just before they took out the lighteners and other things and now are considered medical uses. So these -- the list of categories is the same.

DR. BELSITO: Okay.

DR. BRESLAWEC: Is what Rachel was saying there's a difference between the '94 uses and the 2009? Or is she getting the data elsewhere?

MR. SILBERGELD: Yes.

DR. BRESLAWEC: Okay.

MR. SILBERGELD: That may all be due to a shift in the groupings.

DR. BELSITO: Well, no, her comment with baby -- baby and lip is basically what her comments are -- that some of these ingredients have new uses, but other ingredients within this family, at least cetrimonium bromide had eye uses.

I'm just looking to see if there were lip and baby uses for other members of the family. But it's certainly, you know, when we've seen things like that, I mean, it -- we certainly want to focus on data that would support safety for, you know, particular an eye in terms of ocular toxicity or lip in terms of oral or, you know, with a baby and things that we might be marginal about absorption on would create more of a concern with products that are used extensively on infant skin. It would, at least according to some studies be more absorbed if -- that's a good pick up. I'm not seeing any real reported uses for baby product uses here before.

DR. SNYDER: There's some -- well, there's other, like on Table 8.

DR. BELSITO: I haven't gotten there yet. Table 8?

DR. SNYDER: Yeah, at the bottom of 43. Two or 3 percent.

MS. BECKER: Baby shampoo (inaudible) cetrimonium chloride of 0.4. Cetrimonium chloride

got other. We have six listed.

DR. BELSITO: Okay. So we'll keep that in mind as we go forward.

Any other comments?

DR. SNYDER: So this is going to be reopened?

DR. BELSITO: This is going to reopened to add the ingredients in Table 1 through 4, except for the four ingredients in Table 1: The tosylate, the two saccharinates, and the triphenoxide.

DR. SNYDER: Trichlorylphenoxide.

DR. BELSITO: Trichlorophenoxide.

DR. SNYDER: And then are we going to partially formulate the data needs at this point? I mean, we've got (inaudible).

DR. BELSITO: Well, I think that the data needs that we have are for Carol to go out and get what the Europeans have that we can freely get and figure out what the hang up is.

DR. EISENMANN: It's publicly available on the Internet.

DR. BELSITO: Okay. Figure out what the hang up is with choline. And to go and look for concentrations, you know, scour industry for concentrations of use. Method of manufacturing and impurities I think is --

DR. EISENMANN: Yes. That's (inaudible).

DR. BELSITO: We need as much as we can --

DR. EISENMANN: There's an HPV thing on some of these ingredients that might have some of that information.

DR. BELSITO: Okay. And just general, you know, rewrites based upon Dan's comments about, yeah, the broad comments as to what these chemicals are and how they're used certainly would be nice. I think that's where we're at right now.

Paul, did you have some additional needs?

DR. SNYDER: The other thing is on page 11 where we have Mexico and then all the South American countries having the limits. We don't

specify again why that is or -- is it irritation or is it --

MS. BECKER: It wasn't in the data I had. Just that there are limits.

DR. EISENMANN: Then you shouldn't be saying (inaudible) for that, too. It's a database that is only available to members.

DR. SNYDER: Because one of them is restricted to 1 percent. So I think we need to either --

DR. EISENMANN: Usually you just click Europe and, I don't know, do you really need all the other countries? Most countries pick up the Europe regulations. I don't know if you need all the other countries, but if you want the other countries you've got to go find the original regulations and not use the IRDB.

DR. BAILEY: Because it's not publicly available.

DR. EISENMANN: Right.

DR. BAILEY: It does reference information that is publicly available, but, you

know, that's what should be --

DR. EISENMANN: It might be in a different language.

DR. BRESLAWEC: We kind of moved away from including a lot of other countries in our summary.

DR. BELSITO: I don't have a problem with getting rid of everything except the -- I mean, traditionally we've done EU and Japan.

DR. BRESLAWEC: Right. And that would --

DR. BELSITO: That's fine with me. Particularly if it's going to require that the writer go back and look at the original material that these countries looked at.

DR. BRESLAWEC: Okay.

DR. BELSITO: Any other comments?

DR. BRESLAWEC: (inaudible) we're trying a different approach, I think, on this one, as you know, and what we included was a draft report. So we would be asking the panel to make a -- to act on the draft report. You can table it or issue an

insufficient data request or issue it as a tentative report if you feel that is warranted.

DR. BELSITO: Well, I think, you know, we're clearly going out as insufficient -- is what we talked about. And what we need are method of manufacturing and impurities.

DR. BRESLAWEC: That material may be available. It's just that it wasn't included in the report. There's no reason to believe that it's not available and --

DR. BELSITO: I understand, but --

DR. BRESLAWEC: -- and that's just something that we can handle as a table report or even incorporate that into --

DR. BELSITO: Then I guess it goes back to, I mean, the arguments that we had whether to table -- I forgot what report at the last meeting that went on forever as to whether that material was available and should be tabled. And John, do you remember? Because you were the one that wanted it tabled.

DR. EISENMANN: Kojic acid?

DR. BELSITO: What?

DR. EISENMANN: Kojic acid.

DR. BRESLAWEC: But that was different because that was information we had to request from -- this is information that I believe we have access to and we just did not incorporate into the report.

DR. BELSITO: I mean, I don't care one way or the other. I mean --

DR. SNYDER: I think I'm okay with saying reopen and we're going to include these ingredients and then we've identified other data needs. And so I think we're maybe a little premature on jumping to the insufficient. So, I mean, I think that's kind of where we're at.

DR. BELSITO: Well, actually, yeah. I mean, that's the whole decision here is to reopen or not reopen. We don't need to make a correction at all, do we?

DR. SNYDER: Correct.

DR. BRESLAWEC: Well, I think you have made the decision. You're going to recommend

reopening. This is unusual because usually you just make that decision and then we prepare a draft report. In this case we're prepared a version of a draft report so you have the option. And I don't think this is the case here. But if you though the draft report was adequate enough you could issue it as a tentative report. And I think you're not there.

DR. SNYDER: No.

DR. BRESLAWEC: So then the question is because you have a draft report you can table it and you can go and collect the data. With the insufficient data I think we have to go to industry with specific requests for data that don't exist, at least not in our information. I think we're saying the data exist; we just haven't put it in the report.

DR. BELSITO: Right. Is that correct, John? I think if we go insufficient they have to go to industry?

DR. BAILEY: It doesn't have to.

DR. BELSITO: Yeah, because we went

insufficient and industry was supplying us with this other ingredient with just sensitization and irritation. And we're going back -- and CIR was going back and getting the information on the alcohols and everything else. It wasn't kojic acid. I'm blanking on it. We'll see it in this report again I think.

DR. LIEBLER: Pelargonic. Pelargonic, I think.

DR. BELSITO: Yes, exactly.

DR. LIEBLER: Pelargonic acid.

DR. BELSITO: I don't care one way or the other. We can just say we're going to reopen it.

DR. SNYDER: I think procedural to me reopening is different than tabling.

DR. BRESLAWEC: Reopening is a whole separate issue.

DR. SNYDER: Right.

DR. BRESLAWEC: And I think you've reached the decision to reopen.

DR. SNYDER: Correct.

DR. BRESLAWEC: We're trying to move the process along a little faster by giving you a draft report.

DR. BELSITO: I understand.

DR. BRESLAWEC: And asking you to act on that.

DR. BELSITO: But I think if we had all of the information, Halyna, we could say we're going to reopen it and P.S., we think it's safe as used.

DR. SNYDER: Right.

DR. BELSITO: But we don't have all the information so I think we -- procedurally it would seem to me we say reopen and then in this case you tried your best to give us a report, but it wasn't there. You got a sense as to what at least this team needs. You'll get a sense as to what the other team needs. And then proceed. And then we'll see it again and then that time we'll say sufficient, insufficient, or whatever.

DR. SNYDER: Right.

DR. BELSITO: So I think maybe what

we'll just say is reopen and these are the ingredients that we want to include.

DR. BAILEY: Well, I think what Halyna is also saying is that for others you're going to do the same thing.

DR. BELSITO: Right.

DR. BAILEY: Right? And so that gives you the option of --

DR. BELSITO: Of reopening.

DR. BAILEY: It's okay.

DR. BRESLAWEC: That's right. It's pretty clear that you don't feel comfortable enough with this report to make it a tentative report. I'm certainly not encouraging that. I'm just bringing it up because I think you're going to see this more and more.

DR. BELSITO: I think it's great. I think, you know, in this case it's just --

DR. BRESLAWEC: That's perfectly understandable.

DR. LIEBLER: So at this point do we need to identify more specifically some of the

data needs that we have?

DR. BELSITO: I think it would be nice again because Halyna's point is they may have not searched the literature or brought in what's in the open public literature at this point. And also just to give industry a heads up, you know, in case that information doesn't exist. You know, this is where we think the deficiencies lie. But we're not -- we're not creating a list yet. You know, in terms of what is insufficient, but in terms of this document we would like to see this data included into this document when we see it.

MS. BECKER: And I can concentrate on looking for it.

DR. BELSITO: Right.

DR. LIEBLER: So then we have some chemical subgroupings within the things that we -- within the compounds that we've agreed to include in this reopened document. And for example, irritation and sensitization data really are all about the simple alkyl chain derivatives here. But some of the ethers and amides, the choline or

carnitine derivatives are not represented there. And we probably need to have representative sensitization irritation data for those subfamilies of this grouping because they actually may be different.

DR. SNYDER: Well, I don't necessarily think so because we're going to go with a (inaudible).

DR. BELSITO: Well, but sensitization (inaudible).

DR. SNYDER: That's what -- I was just referring to sensitization and irritation.

DR. BELSITO: And I think as the report is produced, too, for ease again, a flow sheet within the four chemical groups as to what's available for those groups in terms of sensitization, irritation, absorption or whatever, just so we can see how much we're relying on maybe data from another group to carry a group where there may be virtually no data. And that could give anyone cause based upon what they know. So then I think that's going to be very important to

look at.

DR. BAILEY: I think there's also an important concept here in that if we're adding these groups together -- and I think we're doing a much better job of breaking these out and putting them into groups -- if we get to a point where the data doesn't support one of those subgroups, in other words, you know, that there's enough of a difference, you know, I don't think we ought to put those in an insufficient data box. I think what we should do is cut them out of the report --

DR. LIEBLER: Sure.

DR. BAILEY: -- and then defer those to another separate assessment. So.

DR. LIEBLER: Indeed. And in fact, I think one of the things that could lead to that type of situation is that we're being driven by chemical similarity in large part in making these groupings. But the other logical way to consider this is how they're used in products because that dictates whether they might be in sprays or rinse-offs or leave-ons and so forth. And that

could dictate the types of information we feel are most important to have about sensitization, irritation, and so forth.

DR. BELSITO: Okay. Any other comments? Seeing none I think we're done with the trimoniums.

DR. BAILEY: So what I heard then is sensitization and irritation.

DR. BELSITO: Yeah. That's going to be the biggie and method of manufacturing and impurities, and obviously concentration of use. Okay.

So now to the PMMA group. That's Pink 3.

MS. BECKER: I have the representative from industry here if you have any questions to ask her.

DR. BELSITO: Okay.

MS. BECKER: Mary Phillips.

DR. BELSITO: Okay. We also have a memo from John Bailey reported that the levels of the monomer methyl methacrylate, methyl methacrylate

it is being couched. So, to be perfectly honest with you, I think that that level from the head of the company was ill-advised and is better ignored.

DR. HILL: Well, I wasn't -- as I say, I wasn't suggesting that you respond directly to individual criticisms, but just that any language that lays out the difference in this particular approach to review effectively addresses the concern -- anybody else who has the same concerns.

DR. ANSELL: Yeah. Yeah. We've got to be able to link just why the heck do we think that data for devices, et cetera, has any applicability, and, yes, we will make that lingo.

DR. MARKS: Okay. So we'll -- I'll move that we issue a tentative report tomorrow indicating that this group is safe and then we have those two discussion points about the inhalation particle size and using the medical-grade PMMA toxicity to support the safety of the use of these ingredients in cosmetics.

DR. BERGFELD: Okay.

DR. MARKS: Any other comments? This is

a -- now, I have the next as the trimoniums re-review, yes.

DR. HILL: This was the one that was on my mind when I made the comments this morning.

DR. MARKS: So there were three chemicals in which the safety assessment was published in 1997 for that have set trimonium chlorides and bromide, and then the steartrimonium chloride was found to be safe for use in rinse-off products and safe for use in a concentration up to 0.25 products in leave-on products.

We need to decide one, do we want to reopen this primarily driven that the behentrimonium -- is that how you say that, Alan?

DR. ANSELL: Behentrimonium.

DR. MARKS: Behentrimonium chloride is on the CIR's 2010 Priority List, so we would be looking at this as an add- on to the original report, and then we have some other chemicals also.

So I guess we should start with do we want to reopen it and what do we want to add and

in on page 20, 32, there's a list in Tables 1 through 5 of a large number of ingredients which potentially could be added on or divided out, as you see in Table 1, Table 2, Table 3, 4, and 5.

So do we want to reopen it just for this one compound or do we want to expand it on into the compounds listed in Tables 1 through 5?

DR. SLAGA: Reopen to add related compounds?

DR. MARKS: Okay. Reopen to related compounds.

DR. SLAGA: Related. So.

DR. MARKS: Which would include behentrimonium, since that's the compound at least as high in the priority; correct?

DR. SLAGA: Or anything related to that, too.

DR. MARKS: Or related to that. So, shall we go -- so reopen, and, Ron Shank, does that sound appropriate to you and, Ron Hill, that we reopen it?

DR. SHANK: Yes, it does.

DR. HILL: Yes, reopen.

DR. MARKS: Okay.

DR. BERGFELD: I'm open to opening it. I just wanted to hear from our chemist how he came up with this list. It's enormous.

DR. HELDRETH: Okay. So, you know, behentrimonium was certainly what we were after for a priority list, and certainly the cetrimonium chloride and bromide and the stearonium were something that we reviewed in the past. And so it seemed to make sense if we were going to make the jump to a few carbons longer, and that's really the only difference between steartrimonium chloride and behentrimonium chloride, then why not run the gamut of things that differ mostly by just the differing chain lengths?

And if we look in Figure 1A, we have across the bottom --

DR. MARKS: What page?

DR. HELDRETH: Oh, I'm sorry.

DR. MARKS: What page?

DR. HELDRETH: Page 27. In Figure 1A,

we have across the bottom individual compounds such as laurtrimonium bromide, laurtrimonium chloride, and as we go across the bottom of the page there, those compounds differ by different chain lengths.

Those compounds shown in boxes above, for example, cetrimonium chloride, that first little oddly shaped box above the single compounds, under that one INCI name, it's a combination of those two different chain lengths. And so these boxes kind of place themselves from left to right as to the length of the chemical. So, all they're differing here is by increasing molecular weight, increasing chain length, which ordinarily correspond to differing lipophilicity, polarity, and the ability to be absorbed.

If we move on to Figure 1B, it's the same type of set up, and that's on page 28, except for all of these compounds have an amide functional group within them, and so that's why I separated it out into a separate table. If you have a problem with amides, then, you know, you

make your decision based on that.

Figure 1C is a little bit different in its organization, because all of these compounds have a central core functionality besides the trimonium group, the choline group. So you've got the trimonium group; two carbons next to that you have essentially an alcohol functional group.

And looking at the table, you can see I mapped out ones where there was either an acetate or some sort of ester functionality, or going the other direction, it's just a matter of lengthening chains.

Figure 1D is, again, there's just additional functional group here. These are alkanolamides, so it's an amide like in Figure 1C, but it also has an alcohol functional group dangling off of it.

And then the last one here, 1E, which actually starts on page 31, are glycol functionalized trimoniums.

What's not represented by these tables are the polymers, which, you know, it's, of

course, up to you to decide if they're different or not, but mapping them out in the same way is not necessarily something that straightforward.

DR. MARKS: Well, I think the rule it's got to be a no-brainer applies to this since we are opening and adding on, so we can't use the previous reasoning that we haven't seen this before. So, I think with that in mind, we need to pick the add-ons, which are no-brainers.

And I just want to go back and clarify in my mind was it behentrimonium chloride was that high on the priority list because of its 641 uses, since it had so many uses?

DR. BRESLAWEC: Yeah, behen trimonium was a 2009 -- no, I'm sorry, 2010 priority.

DR. MARKS: Right. Okay. And it's because of uses, not because of a toxic alert? Okay.

Okay. So we can either go use the figures. I like the way you did those, Bart, on page 27 through 31, or we can actually go to the tables on 32. So probably, for me, it's easier

looking down the tables as to what we're going to include.

So on Table 1, the straight chain alcohol trimonium compounds and their salts are there and among that, at the bottom of 32, is behentrimonium. Are there any ones which are more than no-brainers in this list in Table 1, and that extends on to page 33. Is there any that should be eliminated, that with the present safety data, we can just extend it and say these chemicals can be felt to be safe without any further data?

DR. SHANK: On Table 1A, I took out the laurtrimonium trichlorphenoxide, because I don't think we have any data on trichlorphenoxide, and that's a little different from all of the rest.

DR. MARKS: So, now where are you, Ron?

DR. SHANK: Table 1A, page 27.

DR. MARKS: Twenty-seven. Third one down?

DR. SHANK: The third one down.

DR. MARKS: Yes. Okay.

DR. SHANK: I took that one out. Then I

had question marks about the two sacchrinates. If we have any information on skin tox, on saccharin. I don't think we have. Now saccharin's been tested ad nauseum for bladder cancer, but that's a different question than skin. And since we don't have the data on saccharin, I would take that out.

DR. MARKS: And this is on page 30?

DR. SHANK: Page 27 again.

DR. MARKS: Oh, you're back on the -- okay.

DR. SHANK: I'm still on Table 1A. Okay.

DR. MARKS: The chart. Could we go to the chart on page 32?

DR. HILL: Oh. Yeah, they're on page 32.

DR. MARKS: Which one is it?

DR. SHANK: Okay. The third one and the --

DR. MARKS: Yeah, I have the third one, the laurtrimonium trichloride.

DR. SHANK: Just past halfway is. Then

the middle --

DR. MARKS: Oh, yes.

DR. SHANK: Cetrimonium saccharinate.

DR. MARKS: Oh, yeah. Okay. I see.

DR. SHANK: And then second from the bottom --

DR. MARKS: Okay.

DR. SHANK: -- steartrimonium saccharinate.

DR. MARKS: Anything in the straight chain alcohols? Any other ones that should be eliminated? So the rest look okay when we switch over -- when we go over to page 33 and then there are the branch alcohol, which were just two. Are those two again no-brainers?

DR. BERGFELD: Why won't you take in -- take out the other benzene ring there?

DR. ANSELL: Cetrimonium tosylate.

DR. BERGFELD: It's a quaternary ammonium just like the one above that you took out.

DR. ANSELL: Yeah, it's again the --

it's a salt, but you could argue that it's not a simple salt.

DR. HILL: Well, okay. That's the tosylate we're talking about.

DR. ANSELL: Yeah.

DR. HILL: I didn't think that one had been stricken, and you didn't suggest.

DR. ANSELL: I -- Wilma's asking why not --

DR. MARKS: Why not?

DR. ANSELL: -- strike it?

DR. HILL: Because we got done reviewing toluene sulfonates and we I think determined those salts, even though this is an unusual salt, probably don't present an issue.

DR. ANSELL: Okay. But that would be a good rationale.

DR. HILL: I don't know in that case whether there would be any kind of eye and hair membrane penetration issues, but I don't think so.

DR. MARKS: So you would reference the previous report, so I'll need to capture that,

Lillian, with the cetrimonium tosylate. Anything else on page 32 or 33?

DR. HILL: Can you strike -- I didn't fully contemplate these branched ones.

DR. MARKS: Well, that's -- let's see if I -- okay. Well, as we move on, you can think more about those, Ron Hill. How about Table 2, the amides? I can't imagine the size.

DR. SHANK: I said to not include the amides, the alkylamides.

DR. MARKS: Okay.

DR. SHANK: Because those that have already been reviewed have some caveats on leave-ons, as leave-ons, and impurities. And if we include us, then we have to change our conclusion.

DR. MARKS: Okay. And how about the -- and that would go along with the -- everything on page 34, the alkylamidopropyl mixtures, too?

DR. SHANK: Let's see where you are.

DR. MARKS: I'm on page 34. It's the bold type -- the 1, 2, 3, 4, 5, 6h box down there

above babassuamidopropyl trimonium chloride.

DR. HILL: He's on the tables.

DR. MARKS: Yeah, I'm on the tables, not the structures. Page 34.

DR. SHANK: Yes.

DR. MARKS: It's easier for me. The type is larger. Yeah, the type is larger. And it's easier to just go down and cross it that way, Ron. Apologize. You're looking back and forth.

So in that group, the same reasoning? They run over into -- and then we go on to page -- well, we keep on going to --

DR. SHANK: Yes, it would be the same reasoning on those as well.

DR. MARKS: Right. And how about on page 34. If we keep on going, that's -- those amides, the same reasoning there, wouldn't it be, Ron? Just keep on going?

DR. SHANK: Mm-hmm.

DR. MARKS: So, we can get rid of all of Table 2. That extends to the bottom of 36.

MS. BECKER: No, Table 3 starts -- well,

Table 3 starts at the bottom of 35.

DR. MARKS: Oh, does Table 3--oh, okay. I'm sorry. So let's move on. Thank you. I didn't pick that up at the bottom there. So Table 3 --

DR. SHANK: So all of Table 2.

DR. MARKS: Yeah, all of Table 2 is gone. How about Table 3, these alkanol trimonium compounds and related esters, esters, acids, using the no-brainer rule.

DR. HILL: Using the no-brainer rule, those are gone. And I marked no, no, no, no, no all over my little comment page.

DR. BERGFELD: Does that include the ester mixtures, too?

DR. HILL: Let's see. Where are you?

DR. MARKS: The ester mixture would be on the middle page of 36, the cocoylcholine methasulfate. That's what you're referring to; right, Norma?

DR. HILL: I just think as soon as we get into where the choline is there that we're

into something very different, because --

DR. MARKS: Okay.

DR. HILL: -- it's highly likely those esters would hydrolyze unless we're going to capture a lot of information about how that goes.

DR. MARKS: How about Table 4. So we're going to delete all of Table 3. How about Table 4, the glycol trimonium compounds and related ethers and esters? And we have ethers to begin with--well, we have this dihydroxypropyltrimonium chloride and the then the ethers, esters, diesters, alkyl ester.

DR. HILL: So this kind -- this was the basis for my question this morning, when I said how different is the workload? Of course, it changes when you got to go back to the -- dip back into the priority regulations, but how different is the workload to have three sets of three versus one set of nine, because they're clear commonalities. That's why they grouped them as separate tables to where you can say let's review this group together and this group together and

this group together, and it would be I think so much easier to sort out issues of toxicology, and, at the same time, move the others forward; pick up the behenamine without raising complications that I think will arise.

DR. MARKS: So the -- so Table 4, include or delete?

DR. HILL: I had figured that ought to go.

DR. MARKS: Okay. Ron Shank, does that sound reasonable, and Tom?

DR. SHANK: Which table is he at?

DR. HILL: Table 4.

DR. MARKS: And how about -- we're down to Table 5, which are the polymers. And there are homopolymers, copolymers. Bart, you did a lot of sorting out on this. So delete those again? No-brainers?

DR. HILL: To me, definitely.

DR. MARKS: Okay.

DR. BERGFELD: And just a question is, and from a non-chemist, the polymers are larger.

DR. HILL: Yes.
DR. SHANK: They shouldn't absorb them.
DR. BERGFELD: They shouldn't absorb.
DR. HILL: I thought they would present a whole -- yeah, I get your point. I get your point.
DR. SHANK: Yeah, I had to leave those in.
DR. MARKS: Leave them in.
DR. HILL: Leave them in.
DR. MARKS: Leave them in? And the reason to leave them in is just because of what Wilma made that those are not going to be absorbed?
DR. ANSELL: Present no new safety issues.
DR. HILL: Right. That makes sense.
MS. BECKER: Would you clarify Table 4? You said they ought to go? Go with the report or --
DR. MARKS: No, delete it.
MS. BECKER: -- go out?

DR. MARKS: Out. So, if I can summarize this, and I'm going to use the tables, beginning on Table --
DR. SLAGA: We have some more.
DR. MARKS: Oh, is there more than five? I thought.
DR. SLAGA: No, that was five.
DR. MARKS: Yeah, I thought. I was going to say don't create any more, Tom. So, we reopen and we're going to expand the ingredients, including the sentinel ingredient that triggered this, the behentrimonium chloride. So on Table 1, we're going to delete 1, 2, 3 ingredients --
DR. BERGFELD: The two saccharides.
DR. MARKS: -- the two saccharides. How about the laurtrimonium trichlorphenoxide. Wasn't that going to be deleted, too?
DR. ANSELL: Yes.
DR. MARKS: That's three. Table 1, and I will go over these and delete three items, and I'll mention those, Tamara. Am I the one presenting? No, Belsito is. And then we will

delete Table -- all of Table 2, all of 3. Two, 3 are gone. Four is gone. And then 5 is okay. We'll include those. Gone, meaning delete, Lillian.
Any other comments? So we have -- what we're going to add when we reopen it are there some safety issues that we need to address. One of the big issues when you look at the original report was the 0.25 percent in leave-on products, and if you look on page 216 in the discussion, there's some rationale that -- it was agreed that a concentration of 0.25 percent would be an appropriate limit for leave-on products, and, in support of this decision, the Expert Panel also noted that in ocular studies the concentration of 0.1 percent of cetrimonium chloride was non-irritating to the eyes.
And that's basically the rationale. Do we like that?
DR. ANSELL: In the original safety data?
DR. MARKS: Yes. In the original,

because one of the things will be addressing obviously in reopening it not only be the conclusion are we going to change that.
DR. BERGFELD: Maybe you should wait.
DR. MARKS: Yeah.
DR. BERGFELD: Well, just wait to see what -- if you're going to put a restrictive limit on the concentration until you see all the data.
DR. MARKS: Okay.
DR. SHANK: Yeah, just reopen.
DR. MARKS: Okay. Reopen?
DR. SHANK: Don't talk about the discussion and changing the conclusions now.
DR. MARKS: Okay. So we'll reopen. We will include the ingredients that we discussed, primarily the alkyl group and the polymer group.
Okay. Any other comments? Yes.
DR. BRESLAWEC: A procedural comment. We did something a little different here, and you'll probably be seeing more of it. You'll probably be seeing more of this sort of thing. I understand that your decision here is to have us

issue a draft report for your review. We did prepare a draft, draft report, so you would have had an option to issue a tentative report.

Again, I understand your decision to have this come out again as a draft report. I just want to have you be aware that this is something we will be doing more often to give you another option of issuing an ingredient group as a tentative report, if you feel that the information presented is adequate.

DR. BERGFELD: My feeling on this particular ingredient, there are too many add-ons to do that.

DR. MARKS: And I just want to be clear: In the original report, the limit on leave-ons was due to irritation; that was noted in the cetrimonium chloride; is that correct, because, again, it may be when we have all these add-ons, we may have a different conclusion to deal with irritation. It didn't look like it was a sensitizer.

MS. BECKER: When I did the lit search

on this, in collaboration with our toxicologists, they suggest just concentrate on sensitization issue and just about everything on sensitization is in here. So this is the data you have. Yeah, that's been covered.

DR. MARKS: Okay. So we're --

DR. SHANK: Just to -- we've just decided to reopen this, but you anticipated that we would do this and wrote this thing called review and draft amended report ahead of us. So we could move beyond just reopening it, because you've already written the -- is this the staff's report that we're going to consider after reopening this. That's what you're telling us? This thing dated April 6th, 2010 --

DR. BRESLAWEC: No, Dr. Shank.

DR. SHANK: -- which is tomorrow.

DR. BRESLAWEC: We will add the information that you have -- the ingredient groups will be different.

DR. SHANK: Okay.

DR. BRESLAWEC: And your comments will

be incorporated, and whatever questions you ask will be addressed --

DR. SHANK: Okay.

DR. BRESLAWEC: -- in what you get next.

DR. SHANK: Thank you.

DR. BERGFELD: But that -- it doesn't mean you're going out for another lit search on those specific ingredients we decided to include or you've already done that?

DR. ANSELL: Already done that.

DR. BERGFELD: So we will not be getting any more scientific data unless it's unpublished?

DR. BRESLAWEC: It depends on what you add. I do know that we have found some more stuff on the cholines group.

DR. BERGFELD: We took those out.

DR. ANSELL: We took the cholines out.

DR. BRESLAWEC: Yeah, you -- but the final decision is tomorrow, so it's -- but as what you've listed, you've got just about everything that's out there -- yes.

DR. MARKS: That's published?

DR. BRESLAWEC: Yes.

DR. MARKS: So you don't have an SLR with the specific add-ons from the manufacturers?

DR. ANSELL: That's correct. We have no recent unpublished data from industry.

DR. MARKS: Okay. So we have to wait to at least see the response to that request.

DR. ANSELL: Yeah, I think the -- I am concerned, though, about stating to boldly that sensitization is going to be the issue when so clearly in the first safety assessment irritation was the issue. It was -- at least the three compounds that were in the original safety assessment were simply not sensitizers. Those data were fairly clear. They were irritants. So I -- we'll let the data go take us where we need to go in terms of the discussion next time you see this as opposed to prejudging it.

DR. SHANK: Well, why can't we just add these new ingredients to this? Reopen it. Add the ingredients, and we're finished, because we're not changing the conclusion.

DR. ANSELL: I think that may be the case when you see that report next time. I think it will read a lot like what you just said.

DR. MARKS: Okay. So, we'll reopen. We'll add the ingredients that we discussed and then we'll see the new data that is presented to us the next time of the inquiry from industry.

Any other comments about the trimoniums? Bart, thank you for taking us through this chemical playground.

Okay. Next review is the methylacrylate group. This is the first --

DR. BERGFELD: Acetate.

DR. MARKS: -- or acetate. I'm sorry. Thank you, Wilma. The methylacetate group and this is the first time we've seen this. And, again, we have some chemistry involved in terms of the metabolism. So, it's the -- the title at least is "Methyl Acetate, Simple Acetate Esters, and Relevant Metabolites," which include acetic acid. The list is on the memo from Bart, and I think the first question, of course, is, do we want to

re-reviews and trimoniums. Dr. Belsito?

DR. BELSITO: This is a re-review of centrimonium chloride, centrimonium bromide and steartrimonium chloride, that as with all re-reviews now raises the issue as to whether we want to re-review it because of new information and the answer to that is no, or whether we want to open it to add ingredients and the answer to that at least from my panel was, yes, to proceed with opening to add a whole family of trimonium ingredients. Then the question becomes what should that family be? I don't know if you want to discuss that now or at a later point.

DR. BERGFELD: Why don't you continue?

DR. BELSITO: We were presented with five tables of potential trimonium add-ons. Table 1 were the straight-chain alkyl trimonium compounds and their salts and we thought that by and large the ingredients in Table 1 could be added in with the exception of laurtrimonium trichlorphenoxide, the saccharinate, the cetrimonium saccharinate and the steartrimonium

saccharinate, so the two saccharinates we would exclude. And finally, we would exclude the cetrimonium tosylate so that all the other ingredients in Table 1 would be added in.

Table 2 was the amide trimonium compounds and their salts and we felt that those could also be added to the report. Table 3 was the alkanol trimonium compounds and related ethers, esters and acids, and we had some discussion about this. We felt they could be added in. The discussion was mainly about choline chloride, whether that should be added in in light of the fact that it is currently not for use in Europe, but we felt that we would add it in and see what the data was and see what the European issues were.

Table 4 was the glycol trimonium compounds and related ethers and esters, and we felt again that the ingredients in that table could be added in. Finally, Table 5 was the polymers containing trimonium and we felt that those should be excluded from this report.

DR. BERGFELD: Dr. Marks?

DR. MARKS: First of all, I second the motion. We agree that it should be reopened. There wasn't a safety concern, it was expressly for the purpose of adding more ingredients to this re-review.

We had a slightly different conclusion as one might expect in terms of what ingredients to add. Largely Table 1 we agreed. Tosylate was the only one where we thought potentially could be a stay in, but I think that's a relatively small issue. Coming to Table 2, we actually felt that Table 2, Table 3, and Table 4 would all be just carte blanche deleted because we didn't think they were no- brainers, and then we agree that the polymers in Table 5 could be added.

DR. BERGFELD: Excuse me. Added? Dr. Belsito wanted them deleted.

DR. MARKS: You wanted the polymers to be deleted? Interesting. I'm sorry, I misheard that then. Once we get past Table 1 there are complete opposite conclusions. I'll defer to the

two Rons in terms of the no-brainer, why we felt that Tables 2, 3, and 4 should be deleted, and 5 could be included, the polymers.

DR. BERGFELD: Dr. Shank and then Dr. Hill.

DR. HILL: Go ahead.

DR. SHANK: On Table 2 the amides, some of the amides that have already been reviewed have caveats about leave-ons and impurities. So if we add those then we have to change the conclusion and that's not what we're supposed to do so that I would say don't add the amides because then we don't have to deal with the issue of possibilities of impurities and limitations on leave-ons. That's the only one I felt strongly about taking out.

Dr. Hill?

DR. HILL: I agree exactly with what you just said.

DR. BERGFELD: How about Tables 3, 4, and 5?

DR. HILL: What did they conclude about

Table 3, the Belsito group?

DR. BERGFELD: They left them in.

DR. MARKS: Leave them in.

DR. BERGFELD: Dr. Liebler?

DR. HILL: Even the carnitine group you said leave in?

DR. LIEBLER: Correct.

DR. BERGFELD: Is that, yes, leave it in, Dr. Hill?

DR. HILL: I think that would be okay.

DR. SHANK: Table 4.

DR. BERGFELD: Dr. Slaga?

DR. SLAGA: Yes, I thought that Tables 3 and 4 could be left in. The reason we talked about Table 5 is that we're dealing with such large molecules, they're not going to be absorbed and the odds they're going to have some effect are very minimal.

DR. BERGFELD: So there's been a concession. We're leaving in 1, 2, 3, and 4, or 2, 3, 4, and 5?

DR. BELSITO: We're deleting 2, leaving

in 3 and 4, and the question now is 5.

DR. HILL: What did we say about 4?

DR. BELSITO: We're leaving it in I thought.

DR. HILL: I guess my concern with that is that there we have ethers and glycol ammoniums that I wasn't sure if those had ever been reviewed in the smaller molecule toxicology and I didn't see any toxicological data in the report to support that those would be okay, so then we would be down to either definitely insufficient data or possibly changing conclusions. They're not no-brainers from where I sit, and I've thought about this some more overnight whether that was a reason, and I still come to the same conclusion on Table 4. I'm reevaluating after what you all said on Table 3. I can understand and I'm good with that. Table 4, I think there are big gaps in the data for supporting that those are okay.

DR. BERGFELD: Dr. Liebler?

DR. LIEBLER: I guess I don't know if there are big gaps in the data and I'd appreciate

input from anybody else on the panel with more history on these compounds or the components that are the ethers or the glycols.

DR. BERGFELD: Can you comment here. Lillian?

MS. BECKER: This particular set hasn't been thoroughly looked at yet because we're just at what we're going to add.

DR. LIEBLER: I think we were talking about the compounds, the chemical pieces. If I understand Dr. Hill's concern, it's not the entire compound, but the alkyl chain or the ether or glycol chains that are attached to the trimonium piece.

DR. HILL: With the trimethylammonium on the end, yes.

MS. BECKER: If we do leave it in, that data would be in there and you can always change your mind in June.

DR. HILL: So you haven't really done the searches for the biology on that yet?

MS. BECKER: No. There hasn't been a

full search because we're at the point of do we go on or not.

DR. HILL: Then I'm fine with leaving them in at this point.

DR. BERGFELD: So we're left with Table 5. Leaving in? Take out?

DR. BELSITO: I'll cede to Dan. It was Dan's comment for your group to delete that.

DR. LIEBLER: I'll just explain my thinking on that. I thought that the polymers were really dominated by the polymer characteristic rather than the trimonium characteristic of the compound. That might take them a little bit different. However, using the logic we just used for the fact that we actually haven't even looked into the data available on these, I'm perfectly comfortable with leaving them in at this point so that that would be fine with me.

DR. BERGFELD: So it looks like we've left most of the tables in tact except two which were taken out. Correct? Is there any other

discussion? You want us to rediscuss 2?

DR. BAILEY: I'm just saying that I heard one discussed, but I didn't hear the other side discussed, so I'd like to see if that's the consensus of both teams in terms of taking 2 out.

DR. BERGFELD: Dr. Belsito, did you have a comment on Table 2?

DR. BELSITO: I'm assuming, Ron usually does his homework, that it is correct that a number of those amides had conclusions that were restricted and if that's the case, I think we probably should delete them simply because it was the consensus of at least my team that probably where we're going is a safe as used when formulated not to be irritating, and then to start having to give restrictions for the amide members of the family I think would be distracting so that I'm comfortable deleting Table 2 based upon that, that I wasn't even thinking that, yes, there would probably be some restrictions on the amide family.

DR. BERGFELD: With the exception that you've made openings for the other tables and the

fact that you haven't looked at any of the data, did you consider looking at the data and then excluding, Dr. Belsito or Dr. Marks?

DR. BELSITO: This is going to be a huge report and I don't want Lillian to waste a lot of her time. What I would suggest is if she would check to in fact verify that at least several of the amide groups have restrictions in their conclusions and if that's the case then delete the table.

DR. BERGFELD: Dr. Marks? Are you okay with that?

DR. MARKS: Of course. Don's agreeing with Ron.

DR. BERGFELD: Shall we call for a vote to reopen? I'd like to call for an official vote since we have a motion that's been first and seconded. All those in favor of reopening? Thank you. Unanimous. With discussion including one of the tables to be looked into a little bit more intently and that's Table 2.

Then we're moving on to the next

Draft Amended Report of the Cosmetic Ingredient Review Expert Panel of the Report on the Safety Assessment of

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Trimoniums

June 29, 2010

The 2010 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D; Curtis D. Klaassen, Ph.D.; Daniel Liebler, Ph.D; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Lillian Becker, CIR Scientific Analyst/Writer and Bart Heldreth, CIR Chemist.

Cosmetic Ingredient Review

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INTRODUCTION

A safety assessment of cetrimonium chloride, cetrimonium bromide and steartrimonium chloride was published in 1997.[1] These cosmetic ingredients were found to be "…safe for use in rinse-off products and …safe for use at concentrations of up to 0.25% in leave-on products." A search of the *International Cosmetic Ingredient Dictionary and Handbook* revealed a list of ingredients that are structurally similar to cetrimonium bromide, cetrimonium chloride, and steartrimonium chloride. [2]

Most of these ingredients are quaternary ammonium salts. Cetrimonium chloride is an example of a subcategory of the alkyl quaternary ammonium salts, wherein three of the four substituents on the nitrogen atom comprising the quaternary ammonium are each a methyl group. This gives rise to the "trimonium" naming convention used for many of the cosmetic ingredients addressed in this safety assessment, e.g., cetrimonium chloride, so the overall grouping has been give the designation, trimoniums.

The ingredients in this safety assessment are grouped by their structure and functional groups as either:

- straight- and branched-chain alkyl trimonium compounds,
- amide trimonium compounds,
- alkanol trimonium compounds,
- glycol trimonium compounds, or
- polymers

and are listed in Tables 1 to 5. While some of these ingredients vary only by hydrocarbon chain length, there are also branched ingredients, amides, alcohols, esters, ethers, and polymers.

In general, these quaternary ammonium salts dissociate into their ionic components in aqueous cosmetic formulations. For example, upon application of hair conditioners, the cationic chains are attracted to anionic charges in the skin and hair's protein structure, resulting in a conditioning effect.[3] These charged ingredients are less likely to cross the lipid bilayer of the skin, but tend to be irritating to the skin and eyes.

The data from the original safety assessment of cetrimonium chloride, cetrimonium bromide, and steartrimonium chloride are summarized in the appropriate sections in this safety assessment. Each of the major sections of this report is preceded by a brief summary (in *italic font*) of the information relevant to each of the structural subsets listed in tables 1 to 5 and described below.

Straight- and Branched-Chain Alkyl Trimonium Compounds

The first group of ingredients in this report vary structurally from cetrimonium bromide, cetrimonium chloride, and steartrimonium chloride by alkyl chain residue length, the degree of unsaturation, the existence of chain branching or a combination of these variations (Table 1). Additionally, some of the alkyl residues in this group are derived from botanical sources and are actually mixtures of different chain length salts (e.g., soytrimonium chloride). Furthermore, this first group also varies in the identity of the corresponding anions (e.g., bromide, chloride, methosulfate, and tosylate). A mapping of how these salts vary in length is recited in Figure 1a.

Amide Trimonium Compounds

The second set of ingredients (Table 2) consists of alkyl amides. These ingredients are comprised by varying chain length alkyl residue carboxamides, attached to the trimonium core by a short alkyl chain. In some instances the alkyl residue is derived from botanical ingredients and results in a mixture of salts. Some ingredients containing a carboxamide group have been reviewed by the CIR Expert Panel and include: Cocamidopropylamine oxide ("…is safe as a cosmetic ingredient in rinse-off cosmetic products in the practices of use and concentrations described in this safety assessment, but the data are insufficient to make a determination of safety for use in leave-on cosmetic products"),[4] and isostearamidopropyl morpholine lactate ("…is safe for use as a cosmetic ingredient in rinse-off formulations in the present concentrations and practices of use. The Panel also concluded that the available data are insufficient to support safety in leave-on formulations").[5] Cocamidopropyl betaine is currently under re-review but was originally found to be "… safe for use in rinse-off cosmetic products at the current levels of use. The concentration of use for products designed to remain on the skin for prolonged periods of time should not exceed 3.0 percent. The latter is expressed as a 10 percent dilution of a full-strength Cocamidopropyl Betaine solution that has an activity of 30 percent".[6] Acetamide MEA has also been reviewed and the Panel concluded that "[o]n the basis of the data presented in this report, the CIR Expert Panel concludes that Acetamide MEA is safe as a cosmetic ingredient at concentrations not to exceed 7.5% in leave-on products and is safe in the present practices of use in rinse-off products. Cosmetic formulations containing Acetamide MEA should not contain nitrosating agents or significant amounts of free acetamide".[7]

A mapping of how these amides vary in length is recited in Figure 1b.

Also included in Table 2 are the alkanol amides which vary from the other amides by the presence of an alcohol or related ether functional group. A mapping of how these alkanol (choline) ingredients vary in length is recited in Figure 1c.

Alkanol Trimonium Compounds

The third set of ingredients (Table 3) consists of various alkanols and related ethers, esters and acids. These ingredients are comprised by a choline core. These salts vary either by chain length or by degree of acetyl substitution. In one instance, the alkyl residue is derived from botanical ingredients and results in a mixture of salts. A mapping of how these

ingredients are structurally related is recited in Figure 1d.

Glycol Trimonium Compounds

The fourth set of ingredients (Table 4) consists of various glycols and related compounds. These ingredients are comprised by an ethylene glycol core. These salts vary by chain length, ester or ether functionality, or degree of substitution. The developmental and reproductive toxicity of ethylene glycol and its ethers were reviewed by the Panel concluded that "[m]etabolites of ethylene glycol monoalkyl ethers are reproductive and developmental toxins. In general, these metabolites of concern are not expected to be formed in cosmetic formulations that contain polymers of ethylene glycol."[8] A mapping of how these ingredients are structurally related is recited in Figure 1e.

Polymers

The final group of ingredients (Table 5) consists of various polymers containing trimonium. These ingredients are comprised by homo- and co-polymers with at least one trimonium containing repeat unit.

CHEMISTRY

Physical and Chemical Properties

The calculated and available experimental chemical properties for the included ingredients are in Table 11.

Surfactants, or surface-active agents, by definition have two mutually insoluble portions within the molecule (or ion). Typically, one portion of the surfactant will be soluble in polar solvents, such as water, while the other end will be soluble in less polar solvents, such as organic solvents, like octanol. One particular category of surfactants is the cationic surfactants. While these ion pairs (or salts) have negatively charged counter-ions (anions) (e.g., chloride or bromide), the positively charged cations impart the majority of the surfactant character. Among the cationic surfactants, alkyl quaternary ammonium compounds are the most prevalent. The trimoniums are a subcategory of the alkyl quaternary ammonium surfactants, wherein three of the four substituents on nitrogen, comprising the quaternary ammonium, are each methyl.

Typically, the manufacture of trimoniums occurs by the reaction of a tertiary amine (e.g., a nitrogen atom with two methyl groups and one alkyl group bonded to it) with a classic alkylating agent, such as a methyl halide or dimethyl sulfate.[9] For example, behentrimonium sulfate could be prepared by the addition of N,N-dimethyldocosan-1-amine to dimethyl sulfate. Mixtures, like ceteartrimonium chloride (a mixture of cetrimonium chloride and steartrimonium chloride), are often synthesized by the addition of various haloalkanes (e.g., a cetyl halide and a stearyl halide) to trimethylamine.[10]

Straight- and Branched-Chain Alkyl Trimonium Compounds

The first group of trimoniums in this report, as seen in Table 1, consists of cations which are each comprised of a nitrogen atom bonded to three methyl groups and a simple alkyl chain, which can vary in length from twelve carbons (e.g.,

laurtrimonium bromide) to twenty-eight carbons in length (e.g., octacosatrimonium chloride) (see also Figure 1a). All of the straight-chained trimoniums in Table 1 are waxy-solids at human physiological temperatures. The branched-chained trimoniums in Table 1, however, are liquids at the same temperatures. Generally, water solubility and volatility decrease and melting/boiling points increase as chain length is increased.

One example of the trimoniums represented in Table 1, behentrimonium chloride, is a waxy solid and is dispersible in water. Behentrimonium chloride in isopropanol or cetearyl alcohol (concentrations not provided) is stable but is incompatible with strong oxidizing agents.[11] When mixed with cetearyl alcohol (concentration not provided) behentrimonium chloride is a white solid with a specific gravity < 1.[12] Behentrimonium chloride has plant sources that do not contain any genetically modified organisms.[13] It is made through the process of quaternization of behenyl dimethylamine with methyl chloride, in 30% dipropylene glycol.

Amide Trimoniums Compounds

The second group of trimoniums in this report, as seen in Table 2, only differ from the first group by the addition an amide function group to the alkyl chain (see also Figures 1b and 1d). It was reported to be a general trend that incorporation of an amide group into a surfactant will lower the irritation potential of the trimonium.[9,14]

Alkanol Trimonium Compounds

The third group of trimoniums in this report, as seen in Table 3, differ from the first group by the addition of an ethoxy functional group attached to the trimonium core nitrogen (see also Figure 1c). The simplest of these, and a major metabolite of all of the other members in the group, is choline chloride. Choline chloride was reported to not be not volatile at 21ºC and stable under ordinary conditions of use and storage.[15] It may produce carbon monoxide, carbon dioxide, nitrogen oxides, and hydrogen chloride when heated to decomposition. It was reported to be incompatible with strong oxidizers.

Within this group are the choline ethers and esters, with various chain lengths, which are crystalline solids. Also within this group are the carnitine acids and esters. The carnitines differ by the attachment of an acid or ester functional group at the hydroxyl carbon of the choline core, and are also solids.

Carnitine is an amino acid derivative found in high energy demanding tissues and was reported to be an essential cofactor for the transport of long-chain acids across the inner mitochondrial membrane into the mitochondrial matrix.[16] Carnitine was reported to be stable under normal temperatures and pressures.[17] It was reported to be incompatible with strong oxidants, and exposure to moist air or water. Carnitine decomposes into nitrogen oxides, carbon monoxide, carbon dioxide, and nitrogen.

Glycol Trimonium Compounds

The fourth group of trimoniums in this report, as seen in Table 4, differ from the first group by the addition of a dihydroxyalkyl functional group (or glycol) attached to the trimonium core nitrogen (see also Figure 1e). Dihydroxypropyltrimonium chloride is the simplest of these, and a major metabolite of each of the esters. Included within this group are ethers, esters and a diester of dihydroxypropyltrimonium chloride.

An example of the ether derivatives, behenoyl PG-trimonium chloride was reported to be considered stable.[18] There was reported to be a maximum of 2% amines and 25 ppb nitrosamines in behentrimonium chloride.[13] Additionally, there was reported to be a maximum of 10 ppm of heavy metals (< 1 ppm each) including Ni, Cr, Co, Cd, Hg, Pb, As, and Sb, and methylene chloride may be present at < 1ppm.

Polymers

The fifth and final group of trimoniums in this report, as seen in Table 5, differ from the all of the other groups by their incorporation into a polymer backbone. The molecular weights and various physical properties of the trimonium polymers can vary greatly based on the polymerization conditions utilized in their synthesis. Accordingly, molecular weights of the individual monomer units are provided instead.

One example of these, polyquaternium-28, was reported to be 100% ionized in water and has an infinitely small pK.[19] The amide group from the precursor behaves as a weak base. Polyquaternium-28 was reported to be incompatible with strong oxidizing agents and reducing agents. This polymer was reported to be used as an aqueous solution at 20%. Another example, polyquaternium-33 was reported to be stable under normal conditions but decomposes into oxides of carbon and nitrogen including ammonia and hydrogen chloride.

Other

There were no physical properties found for: acetyl carnitine, acrylamidopropyl-trimonium chloride/acrylates copolymer, babassuamidopropyltrimonium chloride, babassuamidopropyltrimonium methosulfate, ceteartrimonium chloride, cinnamidopropyltrimonium chloride, cocamidopropyltrimonium chloride, cocotrimonium chloride, cocotrimonium methosulfate, cocoylcholine methosulfate, carnitine HCl, hydrogenated palmtrimonium chloride, hydrogenated tallowtrimonium chloride, lactamidopropyl trimonium chloride, octacosatrimonium chloride, olivamidopropyltrimonium chloride, palmamidopropyl trimonium methosulfate, and shea butteramidopropyltrimonium chloride.

Analytical Methods

Cationic surfactants have been determined by colorimetry and by mass spectrometry.[1] Steartrimonium chloride could be identified by gas chromatography, spectrophotometry, and in water with fast atom bombardment mass spectrometry. Carnitine was reported to be detected in urine using chip-based electrophoresis/mass spectrometry (CE/MS).[20]

Impurities

Straight- and Branched-Chain Alkyl Trimonium Compounds

Cetrimonium bromide and myrtrimonium bromide are reported to be 99% pure.[21]

Alkanol Trimonium Compounds

The impurities of choline chloride are reported to be trimethylamine (max 500 ppm), ethylene glycol (500 ppm), organic purities (TMS, glycol, chloroethanol; max 1500 ppm), color (max 50 hazen), heavy metals (i.e., lead; 20 pm).[22] Available sources of carnitine are reported to be > 99% pure.[17]

Available sources of acetyl carnitine HCl are reported to be 98.5% to 100.0% pure.[23] Lead was reported to be present at < 20 ppm and sulfated ash at ≤ 0.30%.

Polymers

Polyquaternium-28 was reported to be >99% pure.[19] The maximum content of the residual monomer was reported to be <1%.

USE

Cosmetic

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), cetrimonium bromide was used in a total of 37 cosmetic formulations at the time of the first safety assessment, 1997 (Table 12).[1] No use concentrations were reported at that time. Currently, VCRP data indicated that cetrimonium bromide was reported to be used in 68 cosmetic products (FDA 2009). A survey of current use concentrations conducted by the Personal Care Products Council (Council) reported a range from 0.1% to 2%.[24]

Cetrimonium chloride was used in a total of 162 cosmetic formulations at the time of the first safety assessment.[1] Currently, VCRP data indicated that cetrimonium chloride was reported to be used in 959 cosmetic products.[25] A survey of current use concentrations reported a range from 0.0008% to 10%.[24]

Steartrimonium chloride was used in a total of 6 cosmetic formulations at the time of the first safety assessment.[1] Currently, VCRP data indicated that cetrimonium chloride was reported to be used in 40 cosmetic products.[25] A survey of current use concentrations reported a range from 0.06% to 4%.[24]

The straight-chain alkyl trimonium ingredients have reported uses mostly in hair care products at 0.0005% to 10% rinse-off at and 0.001% to 4% in leave-on products (Table 13). [24,25] No uses or concentrations of use were reported for ceteartrimonium chloride, cetrimonium saccharinate, cetrimonium tosylate, cocotrimonium methosulfate,

dodecylhexadecyltrimonium chloride, hydrogenated palmtrimonium chloride, hydrogenated tallowtrimonium chloride, laurtrimonium bromide, laurtrimonium trichlorphenoxide, octacosatrimonium chloride, octyldodecyltrimonium chloride, steartrimonium bromide, steartrimonium methosulfate, and steartrimonium saccharinate.

The amide trimonium ingredients have reported uses mostly in hair care products at 0.00001% to 3% in rinse-off and 0.00001% to 2% leave-on products (Table 14). No uses or concentrations of use were reported for: acetamidoethyl PG-trimonium chloride, acetamidoethoxybutyl trimonium chloride, babassuamidopropyltrimonium chloride, hydroxystearamidopropyl trimonium chloride, hydroxystearamidopropyl trimonium methosulfate, olivamidopropyltrimonium chloride, ricinoleamidopropyltrimonium chloride, ricinoleamidopropyltrimonium methosulfate, stearamidopropyl trimonium methosulfate, stearoxypropyltrimoium chloride, and stearamidopropyl trimonium methosulfate.

The alkanol trimonium ingredients and related ethers/esters/acids are mostly used in skin care and make-up products (Table 15).[25] Concentration of use data will be provided based on a survey to be conducted by the Council.

Within the VCRP, there is a listing for carnitine and carnitine-l.[25] Carnitine-l is not an ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* so it is not listed in Table 15. However, carnitine is a mixture of carnitine-d and carnitine-l. Carnitine-l uses may be relevant. Carnitine-l was reported to be used in 1 other hair care product; 2 body and hand creams, lotions, powders and sprays; 3 moisturizers; and 6 other skin care products.

The glycol trimonium ingredients are used in hair and skin care products (Table 16).[24,25] Dihydropropyltrimonium chloride was reported to be used in leave-on products at 0.05%; there were no data available for rinse-off products.

The trimonium polymers are mostly used in hair care products (Table 17).[25] Concentration of use data from the Council is expected.

In the European Union (EU), cetrimonium chloride and steartrimonium chloride were reported to be used as a preservative at up to 0.1%. They are also used in rinse-off hair care products at up to 2.5%, leave-on hair products at up to 1.0% and in leave-on facial cream products at up to 0.5%.[26]

In the EU, behentrimonium chloride was reported to be used as a preservative at up to 0.1%. It was reported to be also used in rinse-off hair care products at up to 5.0% as well as leave on hair care products and facial creams at up to 3.0%.[26]

Non-Cosmetic

Straight- and Branched-Chain Alkyl Trimonium Compounds

Laurtrimonium bromide was reported to be used for the separation and purification of DNA fragments.[27]

A commercial product containing cetrimonium bromide (and other quaternary ammonium salts) was reported to be used as a topical antiseptic.[1]

Alkanol Trimonium Compounds

Choline was reported to be used or potentially used for the treatment of toxicity by *N*-methyl-D-aspartate.[28] Choline was reported to be considered generally recognized as safe (GRAS) by the FDA.

Choline and carnitine are reported to be used as dietary supplements.[29,30]

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Oral

Orally administered cetrimonium bromide was poorly absorbed by the intestinal tract of rat and recovered in the feces.

There were no data on amide trimonium ingredients.

Choline consumed in the diet was reported to be absorbed from the lumen of the small intestine. Choline was reported to be obligatory to human cell survival. Choline was reported to be absorbed in the small intestine and converted to phosphatidylcholine and betaine mostly in the kidneys. Acetyl l-carnitine was reported to be maintained in the human body by dietary intake, some synthesis, and efficient renal reabsorption.

There were no data on glycol trimonium ingredients.

There were no data on the polymer ingredients.

Straight- and Branched-Chain Alkyl Trimonium Compounds

Orally administered cetrimonium bromide was poorly absorbed by the intestinal tract of rats.[1] Most of the test substance was recovered in the feces.

Alkanol Trimonium Compounds

Choline was reported to be consumed in the diet and important to the structural integrity of cell membranes, methylation metabolism, cholingeric neurotransmission, transmembrane signaling, and lipid and cholesterol transport and metabolism.[22] Choline was reported to be obligatory to human cell survival. It was reported to be available in the diet as free choline and as phosphatidylcholines, such as lecithin in egg yolks, vegetables, and animal fat.

Choline consumed in the diet was reported to be absorbed from the lumen of the small intestine using transporter proteins in the enterocyte.[31-34] Choline can be liberated from phosphatidylcholine by pancreatic enzymes.[35] Some metabolism by bacteria to form betaine and methylamines was reported to be required before choline can be absorbed from the gut.[36] The free choline enters the portal circulation of the liver whereas phosphatidylcholine may enter via lymph in chylomicrons.[37]

Choline functions as a precursor for acetylcholine, phospholipids, and the methyl donor betaine.[38,39] The Adequate Intake (AI) for choline, the level that prevents liver damage as assessed by measuring serum alanine aminotransferase levels

was reported to be550 mg/day of choline for men and 425 mg/day for women. There are no nationally representative estimates of the intake of choline from food or food supplements. Choline in the diet was reported to be available as free choline or was reported to be bound as esters such as phosphocholine, glycerophosphocholine, sphingomyelin, or phosphatidylcholine. The critical adverse effect from high intake of choline was reported to be hypotension, with corroborative evidence on cholinergic side effects (e.g., sweating and diarrhea) and fishy body odor. The Tolerable Upper Intake Level (UL) for adults was reported to be3.5 g/day.

All tissues accumulate choline by diffusion and mediated transport.[40] A specific carrier mechanism transports free choline across the blood-brain barrier at a rate that was reported to be proportional to the serum choline concentration. In the neonate this choline transporter has a high capacity.[41] The rate at which the liver takes up choline was reported to be sufficient to explain the rapid disappearance of choline injected systemically.[42] The kidney also accumulates choline.[43] Some choline from the kidney appears in the urine unchanged but most was reported to be oxidized within the kidney to form betaine.[44] A significant portion of choline was reported to be oxidized to form betaine in the liver and kidney.[45,46]

Choline was reported to be phosphorylated, converted to cytidine diphosphocholine, and then converted to phosphatidylcholine in the predominant pathway for phosphatidylcholine biosynthesis.[47,48] In an alternative pathway, phosphatidylethanolamine was reported to be sequentially methylated to form phosphatidylcholine by the enzyme phosphatidylethanolamine-N-methyltransferase using S-adenosylmethionine as the methyl donor.[49,50] This was reported to be the major, and possibly only, pathway for synthesis of the choline moiety in adult mammals. It was reported to be most active in the liver but has been identified in many other tissues.[51-53] There are no estimates available as to the relative extent of choline obtained from cell turnover.

Acetyl L-carnitine was reported to be maintained in the human body by dietary intake, some synthesis, and efficient renal reabsorption.[54] Dietary carnitine was reported to be absorbed by active and passive transfer in the intestine. Food provides 54% to 87% of carnitine. The kidneys are an important regulator of carnitine homeostasis. At normal levels, reabsorption of carnitine in the kidneys was reported to be efficient (90% to 99% of filtered load). Renal reabsorbtion decreases when the circulating carnitine load increases. Circulating carnitine was reported to be distributing between large and slow turnover (i.e., muscle) and small and rapid turnover (i.e., liver, kidney, and other tissues). At normal dietary intake levels, whole-body turnover in humans was reported to be38 to 119 h.

Dermal

Cetrimonium bromide and cetrimonium chloride did not penetrate the skin.

Acetamidoethyl PG-trimonium did not penetrate the skin well

Choline chloride do not penetrate the skin well

There were no data on the glycol trimonium ingredients.

There were no data on the trimonium polymer ingredients.

Straight- and Branched-Chain Alkyl Trimonium Compounds

A percutaneous absorption study showed that 59% of 1% cetrimonium bromide penetrated rat skin after 15 min; 0.93% of 0.5% cetrimonium bromide in a hair rinse formulation penetrated after 5 min of exposure followed by rinsing; and 3.15% of 3.0% cetrimonium bromide in water penetrated after 15 min of exposure.[1]

Dehyquart A-CA (25% cetrimonium chloride in a 3.5% emulsion; 25 mg/cm^2 100 mg on 4 cm^2) was applied to the dermatomed, thawed, full thickness skin (1000 μm; n = 6) of the back and flank of castrated male pigs in a diffusion chamber for 30 min.[55] The test substance was then washed off and the receptor fluid sampled up to 72 h. At 72 h, the amount of test substance in the receptor fluid was below detection limit, 0.7 ± 0.6% in the stratum corneum, 0.3 ± 0.3% in the dermis, 1.0 ± 0.9% total in the skin, 90.2 ± 4.5% in the rinsing solution, 17.1 ± 6.2% in the spatula/swabs/pipette, and 107.4 ± 6.1% total in the apparatus. Total recovery was 108.4 ± 6.3%. The authors concluded that cetrimonium chloride may not be systemically available by a dermal route.

Amide Trimonium Compounds

A manufacturer reported that acetamidoethyl PG-trimonium was not expected to be absorbed through the skin or be toxic from dermal contact.[56] No further information was provided.

Alkanol Trimonium Compounds

Full thickness human skin (n = 12) was used in a Franz cells to test the penetration of radio-labeled choline chloride (5%) with and without occlusion.[57] Samples were taken up to 24 h. At 24 h, 0.457 μg/cm^2 choline had penetrated into the receptor chamber for occluded skin and 0.383 μ/cm^2 for unoccluded skin, 0.127% and 0.110% of the applied dose, respectively. There was no statistical difference in these results. Total absorption (epidermis, dermis, and receptor fluid) was 7.42 μg/cm^2 (1.9%) and 13.86 μg/cm^2 (3.43%) for occluded and unoccluded skin. Most of the choline remained in the epidermis and dermis. The authors concluded that choline chloride has a low potential for percutaneous absorption.

Intravenous and Subcutaneous

Cetrimonium bromide was rapidly excreted in the urine and feces.

There were no data on amide trimonium ingredients.

After carnitine was injected into pregnant mice, the highest concentrations of carnitine were in the liver, placenta, kidney, myocardium and choroid plexus in the dam and the fetuses.

There were no data on glycol trimonium ingredients

There were no data on the trimonium polymer ingredients.

Straight- and Branched-Chain Alkyl Trimonium Compounds

Cetrimonium bromide was rapidly excreted in the urine and feces.[1]

Alkanol Trimonium Compounds

[^{14}C]Carnitine (100 µCi/kg) was injected i.p. into pregnant CD-1 mice on day 17 of pregnancy.[58] At 1, 2, 3, and 6 h after the injection, the mice were killed and a full body x-ray was performed. The highest concentrations of carnitine were in the liver, placenta, kidney, myocardium and choroid plexus. No carnitine was observed in the brains of the fetuses or the dam. There was carnitine in the fetuses but than in the dam, but the distribution was similar and increased with time. Carnitine crossed the placental barrier.

Hepatic Metabolism

Palmitoyl-L-carnitine was reported to be hydrolyzed the human liver, mainly associated with the mitochondria.[59]

Miscellaneous Studies

Penetration Enhancement and Inhibition

Cetrimonium bromide enhanced dermal penetration at concentrations below 0.5% and inhibited penetration above 1.0%.

There were no data on amide trimonium ingredients

Palmitoyl carnitine enhanced dermal penetration; acetyl carnitine (with a shorter alkyl chain) did not.

There were no data on glycol trimonium ingredients

There were no data on the trimonium polymer ingredients.

Straight- and Branched-Chain Alkyl Trimonium Compounds

Cetrimonium bromide (in an emulsion) enhanced penetration of phenylazoaniline (pH 7.0), benzocaine (pH 7.0), and benzoic acid (7.0%) up to 0.5% in a Franz cell using dialysis or hydrophobic polydimethylsiloxane membrane (PDMS) membranes.[60] Concentrations above 0.5% were less effective until penetration was inhibited at ≥ 1.0%. Cetrimonium bromide inhibited penetration of benzoic acid (pH 3.0) and phenol (pH 7.0). The authors suggested that micellar solubilization of lipophilic model drugs resulted in a reduction in membrane transport model drug-CTAB complexation at the oil-water interface and in the continuous phase reduced rates of transport of phenylazoaniline and benzoic acid.

Alkanol Trimonium Compounds

Palmitoyl carnitine (0.2 mM) was reported to enhance the penetration of Lucifer yellow and ruthenium red across Caco-2 monolayers by ~10-fold and ~20-fold, respectively.[61] Acetyl carnitine (with a shorter alkyl chain) did not enhance penetration. Palmitoyl carnitine did not enhance the penetrations by PEG 4000. The authors suggest that since there was no damage to the epithelium observed and there was rapid reversal of the effects with the removal of palmitoyl carnitine, the penetration enhancement was not due to cell lysis.

Nasal administration of palmitoyl carnitine (20%) simultaneously with human growth hormone increased the peak penetration by 260%, area under the absorption curve by 64%, and bioavailability by 12.2% in male Wistar rats (n = 5).[62]

Cytotoxicity

Mixed results were reported for the cytotoxicity of laurtrimonium chloride, cetrimonium bromide, cetrimonium chloride to hepatocyte and, erythroleukemic cells. Cetrimonium chloride promoted cell growth below 0.1 µg/ml and was toxic above 3 µg/ml in keratinocytes.

There were no data on amide trimonium ingredients.

There were no data on alkanol trimonium ingredients.

There were no data on glycol trimonium ingredients

There were no data on the trimonium polymer ingredients.

Straight- and Branched-Chain Alkyl Trimonium Compounds

The lethal concentration of laurtrimonium chloride for rat primary hepatocytes was > 0.048 µl/ml.[63]

Human K562 erythroleukemic cells were incubated with cetrimonium bromide (0.1 to 10 µM) for 5 days (n = 3).[64] Cell growth decreased in a dose dependent manner compared to controls. When in a liposome suspension or micellar solution, cell growth decreased in a dose dependent manner; the IC_{50}'s were 0.88 and 0.62 mM, respectively.

Human keratinocytes from foreskins were incubated in cetrimonium chloride for 3 days.[65] Metabolism was then measured using tetrazolium dye. Concentrations > 3 µg/ml completely inhibited dye reduction. At 0.8 µg/ml, there was no inhibition of dye reduction. Concentrations between 0.01 and 0.1 µg/ml enhanced dye reduction. Measurement of DNA content revealed that at these low concentrations, cetrimonium chloride had a stimulatory effect on cell proliferation.

Intestinal Effects

Straight- and Branched-Chain Alkyl Trimonium Compounds

Intestines from adult male Wistar rats were incubated in cetrimonium bromide (5×10^{-5} and 1×10^{-4} l).[66] Examination showed many discharging or empty globlet cells. There was a tendency to swelling of more epithelial cells in the extrusion zone. Otherwise, the sacs did not differ much from incubated controls. The high dose group exhibited separation and

sometimes disruption of mitochondrial christae.

Bacterial Effects

Straight- and Branched-Chain Alkyl Trimonium Compounds

Laurtrimonium bromide was found to inhibit the adherence of bacteria on catheters better than controls and tridodecylmethylammonium chloride and as well as tridodecylammonium chloride.[67]

The minimum inhibitory concentration (MIC) of cetrimonium bromide was 16 μ/ml for *E. coli* and 128 μg/ml for *Pseudomonas aeruginosa*.[68] The authors suggested that cetrimonium bromide was able to disrupt membrane function of Gram negative bacteria. In addition to and simultaneously with this disruption, this ingredient can also chelate K_+ ions from the bathing medium.

The EC_{50}s for cetrimonium bromide and laurtrimonium bromide for *Salmonella typhimurium* was $4.88 \pm 0.08 \times 10^{-6}$ M and $75.00 \pm 3.90 \times 10^{-6}$ M, respectively.[69] The MICs were 1.65×10^{-4} and 4.86×10^{-4} M, respectively.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

The oral LD_{50} of straight- and branched-chain alkyl trimoniums ranged from 490 to 5000 mg/kg for rats and 400 to 633 mg/kg for mice.

The oral and dermal LD_{50} of acetamidoethyl PG-trimonium for rats was reported to be > 2000 mg/kg.

Oral LD_{50} was reported to be between 3150 and ≥ 5000 mg/kg for choline chloride in rats and 3900 and 6000 mg/kg in mice.

For behenoyl PG-trimonium chloride, the oral LD_{50} was reported as 3700 and > 2000 mg/kg for rats, 3200 mg/kg for rabbits, and 2800 mg/kg for guinea pigs.

The oral LD_{50} of quaternium-28 for rats was reported to be> 5 g/kg.

Straight- and Branched-Chain Alkyl Trimonium Compounds

The oral LD_{50} of laurtrimonium chloride in Sprague Dawley CD rats (n = 5) was 490 mg/kg (confidence interval 420 to 570 mg/kg) in one study and 560 mg/kg (500 to 630 mg/kg) in another.[63]

The oral LD_{50} of 40% w/v cetrimonium chloride was 1000 mg/kg for rats.[1] In Swiss-Webster mice, the oral LD_{50} as between 400 and 600 mg/kg.[63]

The oral LD_{50} of steartrimonium chloride was 633 mg/kg for male mice and 536 mg/kg for female mice.

Unpublished studies of the acute oral toxicity of cetrimonium and steartrimonium chloride that were reported by the

European Union's Committee on Consumer Products (SCCP) are shown in Table 18.[55] The LD_{50} for these trimonium ingredients ranged from ~700 to 2970 mg/kg for rats.

A material safety data sheet reported the LD_{50} for behentrimonium chloride for rats to be > 4 g/kg. No further information was provided.[12]

The combined LD_{50} for tallowtrimonium chloride for Sprague-Dawley CFY rats was 1260 (c.i. 1061 to 1496) mg/kg, 1289 (c.i. 1145 to 1444) mg/kg for males, and between 1000 and 2000 mg/kg for females.[63]

Amide Trimonium Compounds

A material safety data sheet states that oral ingestion of acetamidoethyl PG-trimonium may result in irritation of the gastrointestinal tract and gastrointestinal discomfort which may include nausea, vomiting, or diarrhea.[56] Acetamidoethyl PG-trimonium was reported to be slightly toxic if swallowed. No acute target organ toxicity other than what is mentioned above was reported to be expected. The oral and dermal LD_{50} for rats was reported to be > 2000 mg/kg.

Alkanol Trimonium Compounds

Oral LD_{50} was reported to be between 3150 and ≥ 5000 mg/kg for choline chloride in rats.[22] Clinical symptoms after ingestion were restlessness, increased respiration, hypoactivity, convulsions, ruffled coat, staggered gait, and dyspnea. There was some diarrhea. At necropsy, 3 or 10 rats had inflamed lungs.

The oral LD_{50} of choline chloride in mice was reported to be in the range of 3900 and 6000 mg/kg.[22]

The oral LD_{50} of choline chloride was 340 mg/kg for ICR mice and > 200 mg/kg for Sprague-Dawley rats.[70]

The oral LD_{50} of choline HCl in Swiss CD-1 holoxenic mice was 3900 mg/kg.[71] All animals showed salivation, lacrimation, respiratory depression, and convulsions prior to death. The maximum cholinergic effects were observed within the first hour, and all the animals died during the first 24 h of observation. The LD_0 was 2000.

Glycol Trimonium Compounds

For behenoyl PG-trimonium chloride, the oral LD_{50} was reported as 3700 and > 2000 mg/kg for rats, 3200 mg/kg for rabbits, and 2800 mg/kg for guinea pigs.[18]

Polymers

The oral LD_{50} of quaternium-28 for rats was reported to be> 5 g/kg.[19]

Acute Dermal Toxicity

The dermal LD_{50} of cetrimonium chloride was 4.3 ml/kg in rabbits. Tallowtrimonium chloride (4.0 ml/kg) applied to the intact and abraded skin of rabbits resulted in 100% mortality.

There were no data on amide trimonium ingredients.

There were no data on alkanol trimonium ingredients.

The dermal LD_{50} for rabbits was reported to be13,000 mg/kg for behenoyl PG-trimonium chloride.

There were no data on the trimonium polymer ingredients.

Straight- and Branched-Chain Alkyl Trimonium Compounds

The dermal LD_{50} of cetrimonium chloride was 4.3 ml/kg in New Zealand white rabbits (3 males, 3 females); 50% of the rabbits died at the only dose administered.[63] All rabbits exhibited normal behavior until day 3 when the rabbits became lethargic, had depressed reflexes and were cold to the touch. They defecated little or none and had clear fluid coming from their noses and mouths. There was reddening of the nictitating membranes and eyelids. There was substantial weight loss. Skin irritation was noted after 24 h of exposure, including slight to severe erythema, moderate or severe edema, and whitening of the skin. On day 3, there was moderate or severe atonia and moderate or marked coriaceous skin from day 2. Fissuring was observed in 3 rabbits and desquamation in 1. Necropsy revealed brown, liquid fecal matter, lungs adhered to the chest wall, lungs white and filled with white granular pockets, gall bladder enlarged and brownish or clear fluid around the nose and mouth. No visible lesions were observed in the rabbits that survived the 14-day observation period.

Tallowtrimonium chloride (4.0 ml/kg) applied to the intact and abraded skin of New Zealand white rabbits (3 males, 3 females) resulted in 100% mortality between days 3 and 8 of observation.[63] Clinical signs included drooping head and ears, increased respiration rate, increased heart rate, ataxia, depression, excessive salivation, reduced motor reflexes, reduced or lack of feed consumption and defecation. Moderate to skin irritation was observed. There was dilation of dermal blood vessels, gastrointestinal tract, and the brain surface. There was enlarged renal blood vessels and posterior vena cava. The pituitary was dark red to purple.

Three of 6 New Zealand white rabbits (3 males, 3 females) died during the 24-hour dermal administration of tallowtrimonium chloride (4.7 mg/kg).[63] Two more died during the 14-day observation period.

Glycol Trimonium Compounds

For behenoyl PG-trimonium chloride, the dermal LD_{50} for rabbits was reported to be13,000 mg/kg.[18]

Acute Intravenous Toxicity

Straight- and Branched-Chain Alkyl Trimonium Compounds

Intravenous (through tail vein) LD_{50} for female SPF-bred NMRI mice and female Sprague-Dawley rats for various alkyltrimethylammonium bromides range from 2.8 to 20 mg/kg for mice and 5.5 to 44 mg/kg in rats (Table 19).[72] The LD_{50}s increased with the length of the alkyl group. Most animals that died did so within 1 min from apparent respiratory failure. The rest died within 20 min and had tail necrosis.

Alkanol Trimonium Compounds

No data were available on alkanol trimonium compounds themselves. Data were found for choline HCl.

The LD_{50} of choline HCl in Swiss CD-1 holoxenic mice was 53 mg/kg i.v.[71] All animals showed salivation, lacrimation, respiratory depression, and convulsions prior to death. The maximum cholinergic effects were observed within the first hour, and all the animals died during the first 24 h of observation. The LD_0 was 21.5 mg/kg i.v.

Acute Intraperitoneal Toxicity

Glycol Trimonium Compounds

The i.p. LD_{50} of choline chloride (50% powder containing 29% colloidal silicic acid and 21% water) was reported to be 225 mg/kg in male and female mice (calculated for pure choline chloride). Mice died within 2 min at 16oo mg/kg, at 1 h at 640 and 800 mg/kg, and at 1 day at 500 mg/kg. Clinical signs were abdominal position, increased respiration rate, convulsions, dyspnea, exophthalmus, and cyanosis immediately after administration. Occasional adhesions in the liver were observed at necropsy.

Male albino rats (n = 14) injected with choline at 45 mg/kg had 29% mortality; guinea pigs (n = 45) had 20% mortality.[73] When injected with 60 mg/kg, rats (n = 20) had 60% mortality and the guinea pigs (n = 39) had 74% mortality. Animals that lived longer than 30 min survived in most cases.

Acute Inhalation Toxicity

Straight- and Branched-Chain Alkyl Trimonium Compounds

A material safety data sheet (MSDS) included information that acetamidoethyl PG-trimonium in water (concentration not provided) was not expected to be toxic by inhalation.[56] No other information was provided.

Short-term Oral Toxicity

The short-term oral NOAEL was 100 mg/kg for cetrimonium chloride for rats.

There were no data on amide trimonium ingredients.

No effects were observed for mice orally administered choline at 200 mg/kg/d and rats administered 1.2 mmol/kg/k carnitine.

There were no data on glycol trimonium ingredients

There were no data on the trimonium polymer ingredients.

Straight- and Branched-Chain Alkyl Trimonium Compounds

Sprague-Dawley CD rats (n = 10/sex plus 5/sex in high dose group for recovery study) were orally administered cetyltrimethylammonium chloride (24% to 26% cetrimonium chloride; 0, 30, 100, and 300 mg/kg) 5 days/week for a total of 23 or 24 applications.[55] The recovery group was allowed to recover for 27 days. There were no effects to survival, feed consumption, or body weight. The males in the high dose group had increased water consumption compared to controls. No treatment effects were observed through ophthalmological and hematological examination. Clinical chemistry parameters were unaffected by treatment except a small increase (but within the range of historical controls) in serum alanine aminotransferase (ALT) in both sexes in the high dose group. There was a slight increase in absolute and relative adrenal weights and a decrease in absolute and relative spleen weights in males. Necropsy revealed a thickening of the forestomach mucosa, associated with edema and sporadic ulceration in males and females in the high dose group. Inflammatory edema in the forestomach mucosa, sporadic ulceration, and acanthosis up to papillomatous hyperplasia was observed in both sexes in the high dose group at microscopic examination. No histopathological or microscopic alterations were observed in the mid and low dose groups. All treatment-related effects were reversed following the recovery period. The authors concluded that the oral no observed adverse effect level (NOAEL) was 100 mg/kg.

Alkanol Trimonium Compounds

Choline (200 mg/kg) was orally administered to Balb/c mice of both sexes (n = 10) daily for 28 days.[39] Saline served as the control. No effects to body weights, organ weights, hematological parameters, splenic cell counts, pathology of the organs, and clinical bio-chemistry were reported.

Wistar rats (*Rattus norvegicus*) were administered L-carnitine and DL-carnitine (1.2 mmol/kg/d) in drinking water for 7 days.[74] Neither carnitine had an effect on glycemia, food ingestion, or water consumption. Both groups increased free carnitine in the blood.

Short-Term Dermal Toxicity

Straight- and Branched-Chain Alkyl Trimonium Compounds

A 28-day dermal toxicity test using rabbits of 0.5% cetrimonium chloride produced mild, transient dermal irritation.[1]

Short-Term Choline Toxicity

Short-term i.p. administration of choline at 200 mg/kg to mice had no effects to body weights, organ weights, hematological parameters, splenic cell counts, pathology of the organs, and clinical biochemistry. Short-term administration i.p. of choline at 50 mg/kg/d to guinea pigs resulted in lung lesions.

Intraperitoneal

Choline (200 mg/kg) was administered i.p. to Balb/c mice of both sexes (n = 10) every other day for 28 days.[39] Saline served as the control. No effects to body weights, organ weights, hematological parameters, splenic cell counts, pathology of the organs, and clinical bio-chemistry except for increased creatinine levels were reported.

Male guinea pigs (n = 10) were administered choline (50 mg/kg/d) 5 days/week for 8 weeks (40 doses).[75] The controls (n = 5) were untreated. They were then killed and necropsied. The guinea pigs developed lung lesions consisting of peripheral nodules of small cells, neoplastic bronchiolar epithelium, carcinomatous lesions, and changes in the pleural surface.

Intranasal

Choline (200 mg/kg) was administered nasally under light anesthesia to Balb/c mice of both sexes (n = 10) every other day for 28 days.[39] Saline served as the control. No effects to body weights, organ weights, hematological parameters, splenic cell counts, pathology of the organs, and clinical bio-chemistry were observed.

Subchronic Dermal Toxicity

Straight- and Branched-Chain Alkyl Trimonium Compounds

Ammonium, hexadecyltrimethyl-, chloride (54.5% in aqueous isopropanol) was used to dermally administer cetrimonium chloride (0 and 0.5%; 2 ml/kg; 10 mg/kg cetrimonium chloride) to the clipped skin of New Zealand white rabbits (n = 10; 5 males, 5 females) for 5 days/week for 4 weeks.[55] Skin was abraded with a clipper head prior to each application. Treated skin was cleaned with water after 6.5 to 7 h. Two control rabbits died during the study. There were no treatment-related effects to body weight, hematology, organ weight, gross necropsy findings, or histopathology except that treated areas of the skin had mild to marked acanthosis with active mitosis, hyperkeratosis, and necrosis of the epidermis and hair follicles, with some encrustation and exudates. Slight to moderate erythema was observed in all treated rabbits from days 4 to 8; it disappeared in 4 rabbits by day 17. Very slight to slight edema was observed from days 6 to 12 in 4 rabbits; it subsided by day 17. There was intermittent slight edema during week 4 in 2 rabbits and 1 rabbit developed edema on day 20. There was no desquamation or coriaceousness observed. Three rabbits had slight atonia up to week 4. Slight skin fissuring was observed in most of the treated rabbits that typically disappeared by the end of the study. The authors concluded that the skin changes were due to local irritation and not evidence of systemic toxicity. The dermal no observed effects level (NOEL) was 10 mg/kg/d.

Subchronic Intraperitoneal Toxicity

Alkanol Trimonium Compounds

Male albino rats (n = 25) were administered i.p. choline chloride (0, 45, 148.5, 225 mg/kg; 0, 0.1, 0.33 or 0.5 x LD_{50}

of 450 mg/kg) for up to 8 months.[76] The rats were killed at 1, 3, or 8 months and necropsied. After the injections, the rats were initially excited and active, and then became dull and sluggish. Weight gains were similar between groups except for the mid dose at 3 months, which was greater. There was a dose dependent decrease in relative lung weight at 1 month and an increase in the high dose group at 3 months. There was a decrease in relative weight of the liver and thymus at 1 month, which, in the thymus, continued to 8 months. In the high dose group, relative weights of the peripheral lymph nodes were increased. There was a dose dependent reduction in thymocytes at 8 months. Peripheral lymph nodes had increased cell counts in all doses at 1 month and decrease until 8 months. Regional lymph nodes had reduced cell counts at 8 months in the mid and high dose groups. At 3 months in the mid dose group, cuboidal bronchiolar epithelium, collections of lymphoid cells around blood vessels and bronchiols were observed. The high dose group had collections of plasma cells and lymphocytes around bronchiovascular structures.

Chronic Oral Toxicity

Straight- and Branched-Chain Alkyl Trimonium Compounds

Rats administered cetrimonium bromide at 10, 20, and 45 mg/kg/day in their drinking water for 1 year exhibited decreased body weight gain in the high dose group.[1]

Cetyltrimethylammonium chloride (24% to 26% cetrimonium chloride, 45 mg/kg; 10.70 to 11.70 mg/kg) in drinking water for 1 year decreased body weights and growth rates in rats, which was more pronounced in males.[55]

Alkanol Trimonium Compounds

Fischer 344 rats (n not provided) were administered choline chloride (500 mg/kg/d) in feed for 72 weeks followed by 30 weeks of observation.[77] Necropsy was performed at 103 weeks. Survival rates, body weights, and relative liver weights were not affected by treatment. There was no increase in the number of liver nodules, hepatocellular carcinomas, lung tumors, leukemia, or other tumors in the treated rats compared to controls. The NOAEL was ≥ 500 mg/kg/d.

Male CD1 mice were fed choline-rich (1.6%; n = 6), choline-deficient (0%; n = 7), or normal choline (0.36%; n = 9) diets for 20 to 24 months. There were no differences in body weight throughout the experiment. There were no differences in mortalities and these were similar to historical survival for this strain of mice. There were no differences in dendritic spine densities.

Baboons (n = 24; *Papio hamadryas*) were orally administered normal or increased levels of choline (100 or 500 mg/1000 calories) in their feed for 3 to 4 years. Weights were steady or slightly increased throughout the study. Serum transaminases and glutamate dehydrogenase activity were increased in the high dose group. Bilirubin was increased, albumin

was decreased, and total protein was similar in the high dose group.

CD-1 mice were orally administered choline (0 [n = 23] or 1.6% [n = 17]) in feed for 20 to 24 months.[78] The rats were killed and the brains examined. There were not differences in body weights over the course of the experiment. There were no differences in the concentrations of choline in the striatum, hippocampus, or the cortex between groups.

Fischer 344 rats (n not provided) were administered choline chloride (500 mg/kg/d) in feed for 72 weeks followed by 30 weeks of observation.[77] Necropsy was performed at 103 weeks. Survival rates, body weights, and relative liver weights were not affected by treatment. There were no increases in the number of liver nodules, hepatocellular carcinomas, lung tumors, leukemia, or other tumors in the treated rats compared to controls. The NOAEL was ≥ 500 mg/kg/d.

Chronic Intraperitoneal Toxicity

Alkanol Trimonium Compounds

Male albino rats (n = 10) were administered i.p. choline chloride (25 mg in distilled water) 5 days/week.[79] Two of the rats were then killed and the lungs necropsied at 90, 180, and 330 days. Controls (n = 5) were administered saline intratracheally. Three rats died in the treatment group, none in the control group. At necropsy, the lungs were light pink in color at 90 and 180 days. At 330 days, small white patches appeared on the lobes and the cut surface also revealed clear white mass. At 90 days, sections of lung showed cuboidal type of bronchiolar epithelium along with prominent musculature of the bronchioles and blood vessels. Heavy collections of lymphoid cells around bronchioles were observed together with dilation of lymphatic vessels. A collection of macrophages with pigments as inclusions were observed at the pleural surfaces. Few giant cells were observed in the parenchyrna along with adenomatoid changes. At 180 days, the lungs had hyperreactive ciliated bronchiolar epithelium and mucus adhering on the top of the epithelial lining. The muscles around bronchioles and blood vessels were hypertrophied and found in patches. Heavy collections of plasma cells and lymphocytes were around bronchioles and larger blood vessels. The alveolar macrophages were very prominent and laden with yellowish black pigment. Sporadically, adenomatoid changes of bronchiolar epithelium were found which were more prominent at 330 days. Examination of the musculature of the bronchioles revealed prominent eosinophilic characteristic and lumen filled with cell debris with slight thickening of pleura.

Ocular Irritation

In in vivo tests, cetrimonium bromide and cetrimonium chloride was a severe ocular irritant that caused irreversible damage at 25%. Steartrimonium chloride was rated an irritant in several studies. In in vitro tests, laurtrimonium bromide, cetrimonium chloride, steartrimonium chloride, and behentrimonium chloride were rated mild to severe ocular irritants.

Acetamidoethyl PG-trimonium may cause minor irritation with corneal involvement of visual impairment.

Choline chloride was not an irritant. Polyquaternium-28 was rated a minimal irritant. Choline chloride, carnitine and carnitine HCl may be ocular irritants in in vitro tests.

There were no data on glycol trimonium ingredients.

Polyquaternium-33 was reported to be listed an ocular irritant.

Straight- and Branched-Chain Alkyl Trimonium Compounds

Laurtrimonium bromide (2×10^{-3} to 10^{-2}), when placed in contact only with the epithelium side (outside) of the cornea, produced dose-related development of opacity starting at 10^{-3}.[80] Compared to other surfactants tested, the order of efficacy was laurtrimonium bromide > sodium lauryl sulphate > Tween 20. After incubation and opacity reading the epithelium

In a bovine corneal opacity and permeability (BCOP) assay of cetrimonium chloride (10% in minimal essential medium) had a mean score of 66.4 over 12 laboratories.[81] The ratings for this test are: 0-25, mild irritant; 25.1-55, moderate irritant; ≥ 55.1, severe irritant.

In several in vivo tests, cetrimonium chloride was found to be irritating and caused damage to the eyes of rabbits and rats as low as 0.01% and irreversible damage at 25% (Table 20).

In the original safety assessment, cetrimonium chloride was classified as a severe ocular irritant in in vitro studies.[1] In a Draize eye test (n = 3; 10% w/v), the MAS was 69.0[21]. The authors classified the ocular irritation potential of cetrimonium chloride as severe.

In a test comparing the Draize test and a hemoglobin denaturation assay, cetrimonium bromide (2%; 0.1 ml) was rated as a moderate irritant.[82] Cetrimonium bromide was rated as extremely irritating in a Draize test and bovine corneal opacity and permeability (BCOP) assay.[21] In an interlaboratory test comparing the Draize test and a hemolysis assay, the HC_{50} of cetrimonium bromide was 10.1 ± 12.8 μg/ml.[83]

Cetrimonium chloride (50% active ingredient; 10 μl) was applied to the eye of female New Zealand albino rabbits (n = 12).[84] Controls (n = 4) were untreated. Macroscopic examination and in vivo confocal microscopy revealed increased damage scores compared to controls ($p < .05$). Histological examination revealed almost complete denudation of the corneal epithelium. Keratocyte injury was detected deep within the stroma, extending to the corneal endothelium in some eyes. There was marked death of keratocytes.

The IC_{50}s of steartrimonium chloride on rabbit epithelial (SIRC) cells in an neutral red uptake (NRU) assay were 1.93 ± 0.534, 2.22 ± 2.22, 1.74 ± 0.933, 1.96 ± 0.552 µg/ml using culture medium, phosphate buffered saline (PBS), suspension in culture medium, and all 3 combined as solvents, respectively.[85] In the CVS assay, the IC_{50}s were 1.27 ± 0.283, 1.17, 2.11 ± 1.12, 1.58 ± 0.752 µg/ml, respectively. The maximum average score (MAS) for the Draize test was 91.3 with a 24-h average score of 56.3.

Cetrimonium bromide and cetrimonium chloride had MAS scores of 44.00 and 25.50, respectively (0 = nonirritant; 110 = severe irritant).[86] Myrtrimonium bromide has a score of 42.70.

The results of testing steartrimonium chloride (1%, 10%, and 100%) in a hen's egg test-chorioallantoic membrane (HET-CAM) assay and a chorioallantoic membrane-trypan blue staining (CAM-TB) assay were similar to a Draize test (MAS 91.3; 24-h average score 56.3).[87]

Steartrimonium chloride was severely irritating to the eyes of rabbits and guinea pigs.[1] The MAS for steartrimonium chloride (10%) was reported to be91.3 with a 24-h average score of 56.3. In the Chinese hamster lung cell lines that employed the crystal violet staining (CHL-CVS) test, the EC_{50} was 4.20 ± 1.40 µg/ml.[88,89] In a multi laboratory study, the EC_{50} of steartrimonium chloride in the SIRC-CVS assay ranged from 1.74 to 2.11 ± 1.12 µg/ml in the SIRC neutral red uptake assay.[90] In a multi-laboratory test of the EYTEX system, Steartrimonium chloride was a moderate ocular irritant.[91]

Quartamin 60W (28% steartrimonium chloride:cetrimonium chloride, 80:20; 2% in distilled water; 0.1 ml) was tested for ocular irritation in New Zealand albino rabbits (n = 3; sex not provided).[55] No corneal opacity or irititis was observed. Conjunctival irritation was observed up to day 7. Swelling was observed up to 48 h and continued in 2 rabbits until 72 h. All reactions had resolved by day 14. The authors concluded that the mixture at 0.56% produced transient conjunctival irritation.

Behentrimonium chloride (25% in cetearyl alcohol) was reported to bean ocular irritant.[12] SCCP[55] reported several studies of ocular irritation of behentrimonium chloride in New Zealand rabbits that show irritation at 3% and irreversible ocular damage at 10%.

Alkanol Trimonium Compounds

Choline chloride (70% aqueous) was administered to one eye of a male and a female rabbit.[22] Saline was administered to the control eyes. The treated eyes were reddening and tearing after 10 min. Slight reddening persisted for 3 h. No eye irritation or effects to the cornea were observed after day 1 and up to 8 days.

In a BCOP assay of choline chloride (5 mg/ml; 0.5%; pH 5.3), it was not considered an irritant.[92]

Information in an MSDS stated that choline chloride may cause irritation, redness, and pain.[15]

Information in an MSDS stated that carnitine and carnitine HCl may cause eye irritation.[17]

Glycol Trimonium Compounds

According to a material safety data sheet, high concentrations of Acetamidoethyl PG-trimonium may be slightly irritating to the eyes, nose, throat, and lungs.[56] There may be minor irritation consisting of transient redness and/or swelling. Eye contact was expected to cause minor irritation with corneal involvement of visual impairment.

Polymers

An eye irritation test of polyquaternium-28 (20%, 0.1 ml) using New Zealand white rabbits (n = 6) was conducted.[19] Half of the rabbits had their eyes washed with tap water after 30 sec. Average Draize scores were 13.3, 4.0, and 2.0 at 1 h and 1 and 2 days; rinsing the eyes had little effect. Polyquaternium-28 was rated as minimally irritating to the rabbit eye.

Information in an MSDS stated that polyquaternium-33 was listed as a ocular irritant.[93]

Dermal Irritation

Cetrimonium chloride was reported to be a skin irritant at 25%, steartrimonium chloride at 20%, and behentrimonium was not an irritant at 25%.

There were no data on amide trimoniums.

Carnitine, carnitine HCL, and choline chloride may be skin irritants.

There were no data on glycol trimoniums.

Polyquaternium-33 was listed as a dermal irritant.

Straight- and Branched-Chain Alkyl Trimonium Compounds

In the original safety assessment, steartrimonium chloride was positive in in vivo skin sensitization studies.[1]

A dermal irritation prediction test of cetrimonium bromide using 3T6 mouse fibroblast cells and NCTC 2544 human keratinocyte cells in NRU assay and 3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide (MTT) assays was conducted.[94] Cetrimonium bromide had IC_{50}s of 165.66 ± 19.75 and 102.6 ± 3.96 µg/ml for the 3T6 fibroblasts and 203.23 ± 16.23 and 117.87 ± 13.70 µg/ml for the NCTC 2544 keratinocytes, respectively. The authors concluded that cetrimonium bromide was more irritating than synthetic lysine-derived anionic surfactants.

In the original safety assessment, cetrimonium chloride (100%) was classified as a skin irritant in an in vitro study.[1]

Genamin CTAC (29% cetrimonium chloride; 0.5 ml) was tested on New Zealand albino rabbits (n = 3) under occlusion for 4 h.[55] There were no mortality or systemic effects observed. There were slight erythema and edema at 30 min. Grades 2 to 3 erythema and 1 to 2 edema were observed up to 72 h. Dry and brownish patch skin was observed at 48 and 72 h and at 7 days. There was hardened skin at 7 days, ablation of large scales at 7 and 14 days, and shiny skin at 14 days. Grade 2 erythema was observed at 7 and 14 days. Skin reactions had resolved at day 21. The authors concluded that the test substance

was irritating to skin at 29%.

Quartanim 60W25 (25% cetrimonium chloride; 0.5 ml) was tested on New Zealand albino rabbits (n = 3; male).[55] The substance was placed on shaved skin under semi-occlusive dressing for 4 h. There were no mortality or systemic effects observed. Grades 2 to 3 erythema was observed up to 14 days. Grades 1 to 2 edema was observed between 60 min and 7 days. At day 14, no edema was observed in 2 rabbits and grade 2 edema was observed in the third rabbit. Skin dryness was observed from 24 h to 14 days. The authors concluded that cetrimonium chloride was irritating to skin at 25%.

Genamin STAC (79.2% steartrimonium chloride; 0.5 g) was tested on New Zealand albino rabbits for 3 min (n = 3) and 1 h (n = 1).[55] The test substance was applied to shaved skin under semi-occlusion. There were no mortality or systemic effects observed. The rabbit exposed for 1 hr had grade 2 erythema up to day 22 and grade 1 edema up to 7 days. At day 22, pink new skin and a scar were noted. No erythema or edema were observed for the rabbits exposed for 3 min. The authors concluded that steartrimonium chloride at 79.2% was irritating at 4 h of exposure but not at 3 min.

Quartamin 86W (28% steartrimonium chloride:cetrimonium chloride, 80:20) was applied (2% and 20%; 0.5 ml) to the shaved skin New Zealand albino rabbits (n = 3) under a semi-occlusive patch for 4 h.[55] There were no mortality or observed clinical effects. The high dose group had grade 2 erythema up to 72 h then crust formation at day 7. Grade 1 edema was observed up to 72 h. The low dose had grade 1 erythema at 1, 24, and 48 h in 1 rabbit. No edema was observed. The authors concluded that steartrimonium chloride was irritating to the skin at 20% (4.08% active ingredients) and nonirritating at 2% (.408% active ingredients).

Behentrimonium chloride (5% in a solution with 0.5% methylcellulose in purified water; 0.5 ml) was applied to the shaved skin of New Zealand albino rabbits (n = 3) under semi-occlusion for 3 min.[55] There was no mortality or systemic effects observed. There was no erythema or edema up to 72 h. The authors concluded that a 5% solution of the test substance was non-irritating after 3 min of exposure.

Behentrimonium chloride mixed with isopropanol (concentration not provided) was reported in an MSDS to be non-irritating in vitro.[11] Mixed with cetearyl alcohol (proportion not provided; 25%), it was reported to be non-irritating to rabbits.[12] No other information was provided.

Alkanol Trimonium Compounds

According to an MSDS, Carnitine and carnitine HCl may cause skin irritation.[17]

According to an MSDS, Choline chloride may cause irritation with redness and pain.[15]

Polymers

According to an MSDS, Polyquaternium-33 was listed as a dermal irritant.[93]

Adjuvant Effects

Straight- and Branched-Chain Alkyl Trimonium Compounds

Female BALB/c mice were injected s.c. with ovalbumin alone, with saline, or with cetrimonium bromide (1, 10, 100, 1000 μg) followed by 1 or 2 booster doses of ovalbumin.[95] Not only was there no adjuvant effect of cetrimonium bromide, there was a dose dependent suppressive effect of the ovalbumin.

Dermal Sensitization

Cetrimonium chloride at 3% and steartrimonium chloride at 3.192% were not sensitizers. There were mixed results in dermal sensitization tests of behentrimonium chloride.

Acetamidoethyl PG-Trimonium was not known to be a sensitizer.

There were no data for alkanol trimoniums.

Glycol trimonium are

There were no data for trimonium polymers.

Straight- and Branched-Chain Alkyl Trimonium Compounds

A Guinea pig maximization test was performed on Quartamin 60W25 (25% cetrimonium chloride) using Dunkin-Hartley albino Guinea pigs (n = 20; 10 male, 10 female; control group n = 10; 5 male, 5 female).[26] Induction was at 3% (0.75% active) and challenge at 0.5% (0.126% active ingredient). There were no deaths or clinical signs in the test group. At the first challenge, 3 males of the treatment group and 1 female in the control group had mild erythema. Three males and 1 female in the control group also had mild erythema on the vehicle-treated side. At 48 h, no skin reactions were observed. Histopathology on all skin showed erythema. Reactivity to the vehicle was similar in both groups. The authors concluded that the results were unclear.

A Buehler test on Genamin CTAC (30% cetrimonium chloride) using Pirbright white Guinea pigs (n=6).[55] Dermal induction was at 4% (1.27% active) in distilled water; the challenge was at 1% (0.3% active ingredient). There was slight to well-defined erythema and very slight edema at the treatment sites during induction. There were no skin reactions in the treatment and controls groups at challenge. The authors concluded that the test substance was not a sensitizer under these conditions.

In the original safety assessment, steartrimonium chloride (0.75%) was positive in an in vivo skin irritation study.[1]

A Buehler test was performed on Genamin STAC (79.8% steartrimonium chloride) using Pirbright white guinea pigs (n = 20; n = 10 in control group).[55] Induction was at 4% (3.192% active) in ethanol:water on an occlusive patch on clipped skin for 6 h. Induction was repeated on days 8 and 15. The challenge was on day 29 at 1% (0.798%) in isopropanol on a naive site. The patch was left on for 6 h. No clinical signs were observed. During induction, the treated group had slight, well-defined to

severe erythema and very slight to well-defined edema at the treatment area. No skin reactions were observed after the challenge. The authors concluded that the test substance was not a sensitizer under these test conditions. Note that these results are different from those in the original report.

A guinea pig maximization test using Dunkin-Hartley guinea pigs (n = 10; n = 5 in control group) was performed on Quartamin 86W (28% [20.47% active] steartrimonium chloride:cetrimonium chloride, 80:20) in distilled water or Freund's complete adjuvant (FCA; 50%) and water.[55] Induction was 0.1% v/v (0.0204%) by intradermal injection then a topical patch at 5% (1.20%) on shaved skin for 48 h. Challenge was at day 21 with a patch at 10% (2.4%) on the right shoulder and 5% (1.2%) on the left for 24 h. There was well defined or moderate to severe erythema at the induction sites in the test group at 24 and 48 h. Slight erythema was noted at the induction sites of the control group at 24 h and at 48 h in 1 guinea pig. After topical induction, slight to well-defined erythema was noted at 24 h in the test group; no reaction was noted in the control group. No skin reactions were observed at the challenge sites. The authors concluded that the test substance was not a sensitizer under these conditions.

Hartley guinea pigs (n = 20, 10/sex in treated group; n = 10, 5/sex in control group) were treated with a 10% solution of behentrimonium chloride (vehicle not stated) on a 8 cm^2 filter paper patch, applied to clipped skin on the left flank for 6 h, with occlusion on days 1, 8 and 15.[55] During the induction phase, the skin sites were examined for local effects 24 h after each treatment. The challenge exposure consisted of a 0.5% solution of the test substance loaded into a Finn chamber and applied to clipped skin on the right flank for 6 h, with occlusion, on day 29. A second challenge was performed on day 43 due to equivocal cutaneous reactions from the first challenge. One male animal from the treated group died on day 14, but this was considered by the investigators to be unrelated to treatment. A few treated animals (number not specified) showed slight to well defined erythema during the induction phase. After the challenge, grade 1 erythema was observed in 3/19 animals at 24 h and 5/19 animals at 48 h. A grade 1 erythema was observed in 1/19 and a grade 2 erythema in 2/19 animals at 72 h. No reactions were observed in control animals, after the challenge. The authors concluded that behentrimonium chloride was a sensitizer.

A Buehler test for sensitization was performed on Genamin KDMP (77% to 83% behentrimonium chloride) diluted to a 20% solution in ethanol:water (80:20).[55] Female Pirbright white guinea pigs (n = 20 in test group, 10 in control group) were treated with a 20% solution of the test substance on a 2 x 2 cm cellulose patch, applied to clipped skin on the left flank for 6 h, with occlusion on days 1, 8 and 15. During the induction phase, the skin sites were examined for local effects 24 h after each treatment. The challenge exposure consisted of a 0.8% solution of the test substance in isopropanol on a 2 x 2 cm occluded patch, applied to clipped skin on the right flank for 6 h, on day 29. Skin reactions were scored 24 and 48 h after patch removal.

Animals were observed daily for signs of systemic toxicity and body weights were recorded on days 1 and 31. Treated animals showed slight to well-defined erythema and very slight edema at the site of treatment during the induction phase. No skin reactions were observed in the treated or control animals after challenge.

Glycol Trimonium Compounds

An MSDS stated that acetamidoethyl PG-Trimonium was not known to be a sensitizer.[56] No further details were provided.

GENOTOXICITY

Laurtrimonium chloride, cetrimonium chloride, steartrimonium chloride, behentrimonium chloride, and tallowtrimonium chloride were not found to be genotoxic.

There were no data on amide trimoniums.

Choline chloride and polyquaternium-28 were not found to be genotoxic.

There were no data on glycol trimoniums.

Polyquaternium-28 was not genotoxic in a reverse mutation assay.

Straight- and Branched-Chain Alkyl Trimonium Compounds

In a reverse mutation assay using *Salmonella typhimurium*, laurtrimonium chloride (0.004 to 0.4 µl/plate) was not cytotoxic or genotoxic, with or without metabolic activation.[63] In a forward mutation assay using L5178Y/TK+/- mouse lymphoma cells, laurtrimonium chloride (0.0038 to 0.050 µl/ml without metabolic activation and 0.012 to 0.16 µl/ml with metabolic activation) was not mutagenic. In an unscheduled DNA synthesis assay using rat primary hepatocytes, of laurtrimonium chloride (0.004 to 0.1 µl/ml), the results were negative. In a bone marrow cytogentic assay, laurtrimonium chloride (16, 53.3, 160 mg/kg) orally administered to male and female Sprague-Dawley rats for 5 days did not induce an increase in chromosomal aberrations.

Cetrimonium chloride was negative both with and without metabolic activation in an Ames test up to 625 µg/plate, in forward-mutation and reverse-mutations tests at concentrations up to 50 µg/ml, and in a cell transformation assay up to 1.0 µg/ml.[1] Negative results were also obtained in a chromosome aberration test at concentrations up to 3.0 µg/ml without metabolic activation and 10.0 µg/ml in tests with exogenous metabolic activation. Cetrimonium chloride (62.5 µg/plate) and cetrimonium bromide (no concentration provided) were both negative in Ames tests, and cetrimonium chloride (1.0 µg/ml) also was negative in an in vitro cell transformation assay.

Cetrimonium chloride and steartrimonium chloride were not mutagenic in a reverse mutation assay using *S. typhimurium* (TA98 and TA100).[63]

In an in vitro chromosome aberration test, V79 Chinese hamster cells were incubated with cetyltrimethylammonium chloride (24% to 26% cetrimonium chloride; 0.1 to 6.0 µg/ml without metabolic activation; 0.1 to 10.0 µg/ml with metabolic activation).[55] There were no increases in the number of cells with structural aberrations at any concentration with or without metabolic activation.

Salmonella typhimurium strains TA98, TA100, TA1535, T1537 were incubated in Genamin STAC (79.8% steartrimonium chloride at 4, 20, 100, 500, 2500, or 5000 µg/plate in ethanol) with and without metabolic activation.[55] This was repeated with lowered concentrations of test material (0.8, 4, 20, 100, 500, and 2500 µg/plate). The test compound was toxic at 100 µg/plate, with and without metabolic activation. There was no induction of increased number of revertant colonies compared to controls with or without metabolic activation.

S. typhimurium strains TA98, TA100, TA1535, TA1537, TA1538 were incubated in Quartamin 86W (28% steartrimonium chloride:cetrimonium chloride, 80:20; 0.15 to 50 µg/plate in acetone with metabolic activation; 1.5 to 500µg/plate without metabolic activation).[55] The experiment was repeated with lowered concentrations of test material (0.5 to 50 µg and 0.5 to 150 µg, respectively). There were incomplete bacterial lawns at 15 µg/plate without activation and 150 µg with activation. The test substance was toxic at 50 µg/plate, with or without activation. The test substance did not increase the number of revertant colonies compared to controls.

No data are available for behentrimonium chloride alone, but a commercial mixture, Genamin KDMP which contains 77% to 83% behentrimonium chloride has been tested.[55] Genamin KDMP was found not to be mutagenic, with or without metabolic activation, in the Ames assay when tested at concentrations of 4 to 5000 µg active substance/plate in *S. typhimurium* (TA98, TA100, TA1535, and TA1537). Cytotoxicity occurred at 500 µg/plate without S9 and at 2500 µg/plate with S9.

Tallowtrimonium chloride was not mutagenic in a reverse mutation assay using *S. typhimurium* (TA98, TA100, TA1535, TA1537, and TA1538) with or without metabolic activation.[63] In another reverse mutation assay using *S. typhimurium* (TA98, TA100, TA1535, TA1537, and TA1538), tallowtrimonium chloride was cytotoxic at 500 µg/plate and was genotoxic at 50 µg/plate with TA1538 with and without metabolic activation. The authors suggest that the positive result may be due to impurities.

Alkanol Trimonium Compounds

Choline chloride did not produce any gene mutations, clastogenicity, or DNA damage when tested in vitro in studies reported by UNEP (Table 21).[22]

Glycol Trimonium Compounds

An MSDS stated that acetamidoethyl PG-trimonium was not known to be mutagenic. [56] There are no known effects of chronic dermal or oral exposure other than acute effects. No further details were provided.

Polymers

Polyquaternium-28 (20%) was negative in a reverse mutation assay using *Salmonella typhimurium* (TA1535, TA1538, TA98, and TA100) with and without metabolic activation.[19] In a micronucleus assay using the bone marrow cells of mice, Polyquaternium-28 did not induce an increase in bone marrow polychromatic erythrocytes.

CARCINOGENICITY

There were no data on straight and branched chain trimoniums.

There were no data on amide trimoniums.

There were no data on alkanol trimoniums.

There were no data on glycol trimoniums.

There were no data on trimonium polymers.

Glycol Trimonium Compounds

An MSDS stated that acetamidoethyl PG-trimonium was not known to be carcinogenic.[56] No further details were provided.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Laurtrimonium chloride and cetrimonium bromide produced embryonic effects at 50 mg/kg in rabbits when administered orally. There was no evidence of teratogencity by 2.0% cetrimonium chloride in a dermal study using rabbits.

There were no data on amide trimoniums.

After five days of treatment with i.p. administered choline chloride at 80 mg/kg/d, the seminiferous tubules were normal. After 24 days of treatment, a few tubules of stages I-IV were observed on day 2 after treatment termination. The teratogenic NOAEL was below 1250 mg/kg/d in mice. Choline was toxic to male rat reproduction.

There were no data on glycol trimoniums.

There were no data on trimonium polymers.

Straight- and Branched-Chain Alkyl Trimonium Compounds

In an range-finding study of laurtrimonium chloride (20, 50, 100, 200, 400 mg/kg/d), pregnant New Zealand white rabbits (n = 3) were orally administered the test substance from day 6 through 18 of pregnancy.[63] At 25 and 50 mg/kg, 1 in 3 rabbits died; at 100 mg/kg, 2 rabbits died and at 400 mg/kg, all 3 rabbits died. There were embryonic effects observed at 50 mg/kg.

In the main study, laurtrimonium chloride (2, 8, 24 mg/kg) was orally administered to pregnant New Zealand white rabbits from day 6 to 18 of pregnancy. The dams were killed on day 19 and necropsied. There were no developmental or teratogenic effects observe to the rabbits.

In the original safety assessment, cetrimonium bromide (25 mg/kg/d) was not teratogenic in an oral study using rats.[1] Mild embryonic effects were observed at 50 mg/kg/day, but these were attributed to maternal toxicity rather than a teratogenic effect. There were no embryotoxic or teratogenic effects at lower doses. In an intraperitoneal study, cetrimonium bromide interfered with the embryonic development of mice at 10 mg/kg and was lethal to developing embryos at 35.0 mg/kg. Teratogenic effects were observed in both treatment groups. There was no evidence of teratogencity by 2.0% cetrimonium chloride in a dermal study using rabbits. The only adverse effect observed was dermal irritation at the application sites. When tested in a dermal teratogenicity study, 2.5% steartrimonium chloride was not maternally toxic, embryotoxic, or teratogenic.

An MSDS stated that acetamidoethyl PG-Trimonium was not known to be reproductively or developmentally toxic.[56] No further details were provided.

Alkanol Trimonium Compounds

Male rats were administered choline chloride (80 mg/kg/d) i.p. for 12 or 24 days.[96] Another group was administered choline chloride (10 to 12 mg/kg/d) in feed. The rats were necropsied at 2, 5, 8, and 12 days after the treatment period. There were no effects to body weight gain or weights of testes, epididymides, liver, kidney, and adrenals. After 12 days of treatment (one cycle of the somniferous epithelium), epithelial vacuoles, spermatogonia with pyknotic nuclei and cellular debris were observed 2 days after the termination of treatment. Five days after termination of treatment, the seminiferous tubules were normal. After 24 days of treatment, a few tubules of stages I-IV were observed on day 2 after treatment termination. Most spermatocytes were normal with some necrotic pachytene stages with an essential restoration to normal after 12 days.

Male rats (n = 25; strain not provided) were administered choline (25 mg/kg/d) i.p. for 12 or 24 days.[96] At 12 days, spermatogenesis was not changed. At 24 days, pachytene spermatocytes were decreased until day 5 post treatment. Slight proliferation of spermatogonia was observed from day 5 post treatment onward. By day 12 post treatment, tubules showed almost normal cellular associations. The authors suggest that prolonged administration of excess choline may be toxic to male reproduction.

Pregnant mice were administered choline chloride (1250 to 20000 mg/kg/d) in feed on gestations days 1 to 18.[22] All groups but the lowest had reduced maternal body weight gain. All fetuses were resorbed in the highest dose group and no resorbtions in the low dose group. At 4160 and 10800 mg/kg/d, there was 35% and 69% embryonic/fetal lethality. Developmental toxicity was observed in all but the low dose group; there were no increases in malformations observed. A

NOAEL was not determined for teratogenicity due to the lack of pups.

CLINICAL ASSESSMENT OF SAFETY

Absorption, Distribution, Metabolism, and Excretion

There were no data on straight and branched chain alkyl trimoniums.

There were no data on amide trimoniums.

In humans, choline levels in plasma range from 9 to 20 µmol/l. Increased intake of choline may result in a fishy body odor, vomiting, salivation, sweating, and gastrointestinal effects. Restricting choline intake in the diet may result in fatty liver or muscle damage in men and postmenopausal women and organ dysfunction in premenopausal women. Carnitine was reported to be only eliminated from the body via the urine as carnitine or acylcarnitines.

There were no data on glycol trimoniums.

There were no data on trimonium polymers.

Alkanol Trimonium Compounds

Patients with dyskinesia and cerbellar ataxia were treated with choline chloride (150 and 220 mg/kg/d [10 and 16 g/d, respectively] for 2 to 6 weeks).[97] The patients developed fishy body odor, vomiting, salivation, sweating, and gastrointestinal effects.[36,98]

Additional data were available for choline. Fasting levels of choline in the plasma was reported to be around 10 µmol/l, ranging from 9 to 20 µmol/l.[99] A fishy odor from ingested choline has been reported, possibly due to excessive amounts of trimethylamine, a metabolite produced by bacteriological action and formation of methylamines.[36,98]

Total body carnitine was reported to be mostly contained in skeletal muscle carnitine (~20 g of carnitine in a 70-kg man, of which more than 19 g was reported to be in skeletal muscle).[100] The bioavailability of orally administered carnitine was reported to be ~16% to 18% at doses of 1 to 2 g and may be even lower at higher doses.[101,102] Once synthesized or absorbed, carnitine was reported to be only eliminated from the body via the urine as carnitine or acylcarnitines. Renal tubules contain a saturable carnitine transport system that conserves most filtered carnitine, but leads to large carnitine losses if the plasma concentration exceeds 60 to 90 µM.

Suspected and known coronary artery disease patients had blood analyzed after an overnight fast.[103] The average free carnitine was 41.9 ± 8.9 µmol/l; short-chain acylcarnitine, 10.5 ± 5.3 µmol/l; total acid-soluble carnitine, 52.4 ± 9.4 µmol/l, long-chain acylcarnitine, 2.8 ± .7 µmol/l, and total carnitine, 55.2 ± 9.9 µmol/l.

Carnitine was reported to be absorbed at ~25% when consumed orally.[104]

Subjects (n = 8) were orally administered acetyl-l-carnitine (500 mg) in pill form after overnight fasting.[105] Blood samples were collected at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, and 12 h. The area under the curve $(AUC)_{0?8}$ was 9879 ± 3.757 ml/h, $AUC_{0?12}$ was 6.611 ± 3.757 ml/h, maximum concentration was 1.188 ± 1.316 h, mean resistance time was 4.5 ± 0.3 h, elimination half life was 4.2 ± 1.6 h, and the maximum time to reach maximum concentration was 3.1 ± 0.2 h.

Dermal Irritation

Laurtrimonium bromide was dermally irritating in humans at 7.5%. Cetrimonium bromide not an irritant at 1%. Behentrimonium chloride was not irritating at 5.0%.

There were no data on amide trimoniums.

Choline chloride in liquid and bar soap was not sensitizing at 0.5%..

There were no data on glycol trimoniums.

There were no data on trimonium polymers.

Straight- and Branched-Chain Alkyl Trimonium Compounds

Laurtrimonium bromide (7.5%) was applied to the volar surface of the arms of 11 white, healthy subjects for 20 min for 8 consecutive days (excluding weekends, days 5 and 6). An untreated site and a site treated with water served as controls. The amount of irritation increased with time. The TEWL measurement did not decrease after the weekend break and was not back to baseline for 20 days[106] after treatment ended. Erythema was still present until for 23 days.

Cetrimonium chloride was negative in human repeated insult patch tests at concentrations up to 0.25% for 100% active solutions and up to 0.4% for 25% active solutions.[1]

The relative irritancy potential of cetrimonium bromide (100%) was 518 by the cell suspension agar diffusion test. The relative irritation potential of SLS (> 99%) was 995.[107]

Several studies of dermal irritation of cetrimonium chloride are reported in Table 22. It was not an irritant up to 1% and mixed results were reported above 1%.

The irritancy potential of a formulation containing behentrimonium chloride (5.0%, vehicle not provided) was tested in subjects (n = 51; 5 male and 46 female subjects) using a Finn chamber applied to the subjects' backs, with occlusion, for 24 hours.[55] Deionized water was used as the negative control substance. No difference in irritant reactions between treatment and control sites was reported.

Alkanol Trimonium Compounds

Bar soap and liquid body soap, with and without choline chloride (0.5%), was used by people (n = 25) with self-perceived sensitivity to choline chloride (0.5%) for 21 days.[22] Compared to controls there was no difference in cumulative

irritancy.

Dermal Sensitization

Cetrimonium chloride at 0.25% and behentrimonium chloride at 2.4% were not sensitizing in humans. Choline chloride was not sensitizing at 0.5%. Polyquaternium-28 was not sensitizing at 5%.

Straight- and Branched-Chain Alkyl Trimonium Compounds

Slight dermal irritation was observed during the induction phases of experiments but no evidence of sensitization was observed in a repeat insult patch test of cetrimonium chloride (0.25%).[1]

The cumulative irritancy potential of a rinse-off formulation containing behentrimonium chloride (3.4%; 0.2 g) was tested in subjects (n = 104; 18-70 y old).[55] The test sample was applied, with 2x2 cm Webril patches with semi-occlusive covering, to the subjects' upper arm or back for 24 h 3 days/week for three consecutive weeks. The sites were scored for dermal irritation 48 h or 72 h after removal. One subject showed erythema and edema after the first induction patch. No additional induction patches were applied to this individual. Some minimal erythema was observed in two subjects, and some minimal responses were observed at a few induction readings in three subjects. Additional details were not available. A challenge patch (0.2 g) on 2x2 cm Webril patches was applied for 24 h after a 10 to 15 day interval, to a previously unexposed site. No evidence of a sensitization reaction was observed at 24 and 48 h in any of the test subjects.

Alkanol Trimonium Compounds

In a HRIPT (n = 200), choline chloride (0.5% w/v aqueous) was used in the induction and challenge phases.[22] There was no dermal sensitization observed.

Polymers

Polyquaternium-28 (5%, 0.2 ml) was dermally applied under occlusion to human subjects (n = 104) 9 times over 3 weeks.[19] After two weeks, Polyquaternium-28 (5%, 0.2 ml) was reapplied to a naive area and was assessed 24 to 96 h later. There were no signs of irritation or sensitization.

Phototoxicity

Polymers

Polyquaternium-28 (2%; 0.2 ml) was placed on patches and applied to the volar surfaces of the arms of subjects (n = 10).[19] After 24h, one arm was exposed to UV-A for 15 min. The unirradiated arm served as the control. There were no reactions observed at 24 and 48 h.

Photoallergy

Polymers

Polyquaternium-28 (2%; 0.2 ml) was placed on patches and applied to the volar surfaces of the arms of subjects (n = 28) 6 times over 3 weeks.[19] One arm was exposed to UV-A and UV-B irradiation for 75 to 105 sec (depending on skin type) 24 h after each application of the test substance. The unirradiated patches and untreated areas served as the controls. Two weeks after the completion of induction phase, a single application of the test substance (2%, 0.2 ml) followed by irradiation was administered to a naïve site.

Minimal erythema or erythema and/or slight edema were observed in 26 of the irradiated sites during induction which was similar to untreated irradiated sites in 6 subjects. In the challenge phase, minimal erythema was observed in 4 subjects on treated irradiated sites and in 1 subject on a treated, non-irradiated site. No reactions were observed on untreated irradiated sites. Overall, slight irritation was observed on treated skin exposed to UV-A and UV-B irradiation but polyquaternium-28 did not induce contact photoallergy in humans under these conditions.

Oral Toxicity

There were no data on straight and branched chain trimoniums.

There were no data on amide trimoniums.

Carnitine at 2 mg/kg/d and acetyl-L-carnitine at 1 g/d orally caused nausea and vomiting in humans. Choline chloride at 10 g/d caused slight hypertension in one study and fishy odor, vomiting, salivation, sweating, and gastrointestinal effects. Choline did not induce liver toxicity at 6 g/d. Mild, transient signs of Parkinson's disease developed in tardive dyskinesia patients at 12.7 g/d but no other adverse effects at 20 g/d.

There were no data on glycol trimoniums.

There were no data trimonium polymers.

Alkanol Trimonium Compounds

Subjects with hyperthyroidism-related symptoms (n = 5) were orally administered L-carnitine (2 or 4 mg/kg/d) for 90 days.[108] Mild nausea and gastralgia were reported by 2 subjects the first week. No other adverse effects were reported.

Subjects (n = 7) with dementia of the Alzheimer's type were orally administered acetyl-L-carnitine (1 g/d) for 24 weeks.[109] Nausea and vomiting were the only reported adverse effects.

Alzheimer's patients (n not provided) were orally administered choline chloride (10 g/d, 7.5 g of choline).[110] The patients developed slight hypertension.

Additional data were available for choline. Patients, with and without cirrhosis, have been orally administered choline (6 g/d) for 4 weeks with no liver toxicity.[111] Oral ingestion of choline (20 g/d) for 3 to 4 weeks have been associated with depression.[112] Mild, transient signs of Parkinson's disease have been observed in patients with tardive dyskinesia after oral

administration of choline (12.7 g/d).[113] Patients with tardive dyskinesia and Huntington's disease who were orally administered choline (20 g/d) for 4 weeks had no adverse effects.[114]

Case Reports

One woman who had acute contact dermatitis and worked in a garden center patch tested positive for choline chloride (1% in water and petrolatum).[22] Ten control patients were negative.

SUMMARY

The safety assessment for cetrimonium chloride, cetrimonium bromide and steartrimonium chloride was reopened to add structurally similar ingredients that include:

- straight- and branched-chain alkyl trimonium compounds,
- amide trimonium compounds,
- alkanol trimonium compounds,
- glycol trimonium compounds, or
- polymers.

While some of these ingredients vary only by hydrocarbon chain length, there are also branched ingredients, amides, alcohols, esters, ethers, and polymers.

Trimoniums function mostly as hair conditioning agents, antistatic agents, and surfactants. Cetrimonium bromide and myrtrimonium bromide are reported to be 99% pure. Impurities for alkanol trimonium compounds include: trimethylamine, ethylene glycol, organic purities, color, heavy metals. The maximum content of the residual monomer for polyquaternium-28 was reported to be<1%.

The straight-chain alkyl trimonium ingredients that have reported uses were reported to be used mostly in hair care products; they were reported to be used at 0.0005% to 10% rinse-off at and 0.001% to 4% in leave-on products. The amide trimonium ingredients are mostly used in hair care products; they were reported to be used at 0.00001% to 3% in rinse-off and 0.00001% to 2% leave-on products. The alkanol trimonium ingredients and related ethers/esters/acids are mostly used in skin care and make-up products. The glycol trimonium ingredients are used in hair and skin care products. Dihydropropyltrimonium chloride was reported to be used in leave-on products at 0.05%. Choline and carnitine are used as dietary supplements.

Orally administered cetrimonium bromide was poorly absorbed by the intestinal tract of rats. Most of the test

substance was recovered in the feces. Choline consumed in the diet was absorbed from the lumen of the small intestine. Choline was obligatory to human cell survival. Choline was reported to be absorbed in the small intestine and converted to phosphatidylcholine and betaine mostly in the kidneys. Acetyl l-carnitine was reported to be maintained in the human body by dietary intake, some synthesis, and efficient renal reabsorption.

Cetrimonium bromide, cetrimonium chloride, acetamidoethyl PG-trimonium, and choline chloride do not penetrate the skin well. Cetrimonium bromide was rapidly excreted in the urine and feces. After carnitine was injected into pregnant mice, the highest concentrations of carnitine were in the liver, placenta, kidney, myocardium and choroid plexus in the dam and the fetuses.

Cetrimonium bromide enhanced dermal penetration at concentrations below 0.5% and inhibited penetration above 1.0%. Palmitoyl carnitine enhanced dermal penetration; acetyl carnitine (with a shorter alkyl chain) did not.

Mixed results were reported for the cytotoxicity of laurtrimonium chloride, cetrimonium bromide, cetrimonium chloride to hepatocyte and, erythroleukemic cells. Cetrimonium chloride promoted cell growth below 0.1 µg/ml and was toxic above 3 µg/ml in keratinocytes.

The oral LD_{50} of straight- and branched-chain alkyl trimoniums ranged from 490 to 5000 mg/kg for rats and 400 to 633 mg/kg for mice. The oral and dermal LD_{50} of acetamidoethyl PG-trimonium for rats was believed to be > 2000 mg/kg. Oral LD_{50} was reported to be between 3150 and ≥ 5000 mg/kg for choline chloride in rats and 3900 and 6000 mg/kg in mice. For behenoyl PG-trimonium chloride, the oral LD_{50} was reported as 3700 and > 2000 mg/kg for rats, 3200 mg/kg for rabbits, and 2800 mg/kg for guinea pigs. The oral LD_{50} of quaternium-28 for rats was reported to be > 5 g/kg. The dermal LD_{50} of cetrimonium chloride was 4.3 ml/kg in rabbits. Tallowtrimonium chloride (4.0 ml/kg) applied to the intact and abraded skin of rabbits resulted in 100%. The dermal LD_{50} for rabbits was reported to be 13,000 mg/kg for behenoyl PG-trimonium chloride.

The short-term oral NOAEL was 100 mg/kg for cetrimonium chloride for rats. No effects were observed for mice orally administered choline at 200 mg/kg/d and rats administered 1.2 mmol/kg/k carnitine. Cetrimonium chloride at 0.5% produced mild, transient dermal irritation in rabbits.

Short-term i.p. administration of choline at 200 mg/kg to mice had no effects to body weights, organ weights, hematological parameters, splenic cell counts, pathology of the organs, and clinical biochemistry. Short-term administration i.p. of choline at 50 mg/kg/d to guinea pigs resulted in lung lesions.

Short-term nasally administered choline at 200 mg/kg to Balb/c mice had no effects to body weights, organ weights, hematological parameters, splenic cell counts, pathology of the organs, and clinical bio-chemistry. The short-term dermal NOEL was 10 mg/kg/d for rabbits.

Sub-chronic i.p. administration of choline chloride to rats resulted in changes in the relative weights and/or cells of the liver, bronchiolar epithelium, thymus, and peripheral lymph nodes.

Chronic oral administration of cetrimonium bromide at 10 mg/kg/day resulted in decreased body weights in rats. Chronic oral administration of choline had no adverse effects on rats, mice, and baboons. Chronic i.p. administration of choline at 25 mg/d resulted in adverse effects to the lungs.

In in vivo tests, cetrimonium bromide and cetrimonium chloride was a severe ocular irritant that caused irreversible damage at 25%. Steartrimonium chloride was rated an irritant in several studies. Choline chloride was not an irritant. Polyquaternium-28 was rated a minimal irritant.

In in vitro tests, laurtrimonium bromide, cetrimonium chloride, steartrimonium chloride, and behentrimonium chloride were rated mild to severe ocular irritants. Choline chloride, carnitine and carnitine HCl may be an ocular irritants. Acetamidoethyl PG-trimonium may cause minor irritation with corneal involvement of visual impairment. Polyquaternium-33 was listed as an ocular irritant.

Cetrimonium chloride was reported to be a skin irritant at 25%, steartrimonium chloride at 20%, and behentrimonium was not an irritant at 25%.

Cetrimonium chloride at 3% and steartrimonium chloride at 3.192% were not sensitizers. Behentrimonium chloride was a sensitizer at 10%.

Laurtrimonium chloride, cetrimonium chloride, steartrimonium chloride, behentrimonium chloride, and tallowtrimonium chloride were not found to be genotoxic. Choline chloride and polyquaternium-28 were not found to be genotoxic.

Choline administered intragastrically stimulated the growth of focal lesions in female rats with induced partial hepatectomies.

Laurtrimonium chloride and cetrimonium bromide produced embryonic effects at 50 mg/kg in rabbits when administered orally. There was no evidence of teratogencity by 2.0% cetrimonium chloride in a dermal study using rabbits. After five days of treatment with i.p. administered choline chloride at 80 mg/kg/d, the seminiferous tubules were normal. After 24 days of treatment, a few tubules of stages I-IV were observed on day 2 after treatment termination. The teratogenic NOAEL was below 1250 mg/kg/d in mice.

In humans, choline levels in plasma range from 9 to 20 µmol/l. Increased intake of choline may result in a fishy body odor, vomiting, salivation, sweating, and gastrointestinal effects. Restricting choline intake in the diet may result in fatty liver

or muscle damage in men and postmenopausal women and organ dysfunction in premenopausal women. Carnitine is only eliminated from the body via the urine as carnitine or acylcarnitines.

Laurtrimonium bromide was dermally irritating in humans at 7.5%. Cetrimonium bromide not an irritant at 1%. Behentrimonium chloride was not irritating at 5.0%.

Cetrimonium chloride at 0.25% and behentrimonium chloride at 2.4% were not sensitizing in humans. Choline chloride was not sensitizing at 0.5%. Polyquaternium-28 was not sensitizing at 5%.

Polyquaternium-28 was not phototoxic or photoallergic in humans.

Carnitine at 2 mg/kg/d and acetyl-L-carnitine at 1 g/d orally caused nausea and vomiting in humans. Choline chloride at 10 g/d caused slight hypertension in one study and fishy odor, vomiting, salivation, sweating, and gastrointestinal effects. Choline did not induce liver toxicity at 6 g/d. Mild, transient signs of Parkinson's disease developed in tardive dyskinesia patients at 12.7 g/d but no other adverse effects at 20 g/d.

DISCUSSION

This section is to be determined at the June, 2010 Panel Meeting.

CONCLUSION

The original conclusion for cetrimonium bromide, cetrimonium chloride, and steartrimonium chloride was that these ingredients "…are safe for use in rinse-off products and are safe for use at concentrations of up to 0.25% in leave-on products".

REFERENCES

References

1. Andersen FA. Final report on the safety assessment of cetrinonium chloride, cetrimonium bromide, and steartrimonium chloride. *International Journal of Toxicology*. 1997;16195-220.

2. Gottschalck TE and Bailey JE. International Cosmetic Ingredient Dictionary and Handbook. 12 *ed*. Washington, DC: Personal Care Products Council (formerly the Cosmetic, Toiletry, and Fragrance Association.), 2008.

3. Schwan-Jonczyk, A., Lang, G., Clausen, T., Kohler, J., Schuh, W., and Liebscher, K. D. Hair Preparations. 2002. 6th:(A16): pp.99-140. New York: Wiley-VCH.

4. Andersen FA. Amended final report of the safety assessment of cocamidopropylamine oxide. *International Journal of Toxicology*. 2008;27(Suppl. 1):55-62.

5. Andersen FA. Final report on the safety assessment of isostearamidopropyl morpholine lactate. *International Journal of Toxicology*. 1999;18(Suppl. 3):51-56.

6. Burnett CL, Bergfeld WF, Belsito DV, Klaassen CD, Marks Jr.JG, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. Tentative amended safety assessment of the Cosmetic Ingredient Review Expert Panel: Cocamidopropyl betaine. Washington DC, Cosmetic Ingredient Review. 2008. pp. 1-56.

7. Andersen FA. Final report on the safety assessment of acetamide MEA. *Journal of the American College of Toxicology*. 1993;12(3):225-236.

8. Andersen FA. Special report: Reproductive and developmental toxicity of ethylene glycol and its ethers. *International Journal of Toxicology*. 1999;18(Suppl 2):53-67.

9. Dekker M. Reactions and Synthesis in Surfactant Systems. 2001. (100): pp.30, John Texter.

10. Akisada H, Kuwahara J, Koga A, Motoyama H, and Kaneda H. Unusual behavior of CMC for binary mixtures of alkyltrimethylammonium bromides: Dependence on chain length difference. *Journal of Colloid and Interface Science*. 2007;315678-684.

11. Croda Inc. Material safety data sheet; Behentrimonium chloride (in isoporopanol). 2004. pp.1-4.

12. Croda Inc. Material safety data sheet; Behentrimonium chloride (in cetearyl alcohol). 2009. pp.1-4. MSDS.

13. Harmonized information on raw material identification according to TEGEWA (Version 2007). 2008. pp.1-6. Material Safety Data Sheet in German & English.

14. O'Lenick J and Price SNC. Ingredients, Book Two. 1999. (3):

15. Mallinckrodt Baker, Inc. MSDS: Choline chloride. 9-3-2009. pp.1-4. http://www.jtbaker.com/msds/englishhtml/c4092.htm

16. Evangeliou A and Vlassopoulos D. Carnitine metabolism and deficit - When supplementation is necessary? *Current Pharmaceutical Biotechnology*. 2003;4(3):211-219.

17. Arcos Organics N.V. Material Safety Data Sheet: L-Carnitine, 99+%. 10-3-2005. pp.1-5. http://www.coleparmer.com/catalog/Msds/14442.htm

18. Kao Chemicals GmbH. Safety Data Sheet: According to regulation (EC) No. 1907/2006. 2009. pp.1-4.

19. National Industrial Chemicals Notification and Assessment Scheme. [3-(Methacryloyl amino) propyl] trimethylammonium chloride, polymer with N-vinyl-2-pyrrolidone. Australia, 1999. Report No. NA/89. pp. 1-15.

20. Deng, Y., Henion, J., Li, J., Thibault, P., Wang, C., and Harrison, D. J. Chip-based capillary electrophoresis/mass spectrometry determination of carnitines in human urine. *Anal.Chem.%2001.Feb.1;73.(3):639.-46.* (3:639-46).

21. Vian L, Vincent J, Maurin J, Fabre I, Giroux J, and Cano JP. Comparison of three *in vitro* cytotoxicity assays for estimating surfactant ocular irritation. *Toxicology in Vitro*. 1995;9(2):185-190.

22. Organization for Economic Co-Operation and Development. Choline Chloride Cas No: 67-48-1. United Nations Environment Programme Chemicals Branch. 2006. http://www.chem.unep.ch/irptc/sids/oecdsids/67481.pdf. Date Accessed 4-22-2010.pp. 1-135.

23. Parchem. Acetyl-L-carnitine HCl. 2010. pp.1-2. http://www.parchem.com/chemical-supplier-distributor/Acetyl-L-Carnitine-HCL-001767.aspx

24. Personal Care Products Council. Concentration of Use - Acetamidoethoxybutyl Trimonium Chloride, Acetamidoethyl PG-Trimonium Chloride, Acetamidopropyl Trimonium Chloride, Acrylamide/Ethyltrimonium Chloride Acrylate/Ethalkonium Chloride Acrylate Copolymer, Acrylamidopropyltrimonium Chloride/Acrylamide Copolymer, Acrylamidopropyltrimonium Chioride/Acrylates Copolymer, Babassuamidopropyltrimonium Chloride, Babassuamidopropyltrimonium Methosulfate, Behenamidopropyltrimonium Methosulfate, Behenoyl PG-Trimonium Chloride, Behentrimonium Chloride, Behentrimonium Methosulfate, Behenyl PG-Trimonium Chloride, Cetrimonium Bromide, Cetrimonium Chloride, Cetrimonium Methosulfate, Cetrimonium Saccharinate, Cetrimonium Tosylate, Ceteartrimonium Chloride, Cinnamidopropyltrimonium Chloride, Cocamidopropyltrimonium Chloride, Cocotrimonium Chloride, Cocotrimonium Methosulfate, Dihydroxypropyltrimonium Chloride, Distearoylpropyl Trimonium Chloride, Dodecyihexadecyltrimonium Chloride, Galactoarabinan Hydroxypropyltrimonium Chloride, Hydrogenated Palmtrimonium Chloride, Hydrogenated Tallowtrimonium Chloride, Hydroxystearmidopropyl Trimonium Chloride, Hydroxystearamidopropyl Trimonium Methosulfate, Isostearoyl PG-Trimonium Chloride, Lactamidopropyl Trimonium Chloride, Lauroyl Ethyltrimonium Methosulfate, Lauroyl PG-Trimonium Chloride, Laurtrimonium Bromide, Laurtrimonium Chloride, Laurtrimonium Trichiorophenoxide, Locust Bean Hydroxypropyltrimonium Chloride, Myristoyl Ethyltrimonium Methosulfate, Myrtrimonium Bromide, Octacosatrimonium Chloride, Octyldodecyltrimonium Chloride, Oleoyl PG-Trimonium Chloride, Olivamidopropyltrimonium Chloride, Palmamidopropyl Trimonium Methosulfate, Palmitamidopropyltrimonium Chloride, Palmitoyl Ethyltrimomum Methosulfate, Palmitoyl PG-Trimonium Chloride, Ricinoleamidopropyltrimonium Chloride, Ricinoleamidopropyltrimonium Methosulfate, Shea Butteramidopropyltrimonium Chloride, Soytrimonium Chloride, Stearamidopropyl Trimonium Methosulfate, Stearoxypropyltrimonium Chloride, Stearoyl Ethyltrimonium Methosulfate, Stearoyl PG-Trimonium Chloride, Steartrimonium Bromide, Steartrimonium Chloride, Steartrimonium Methosulfate, Steartrimonium Saccharinate, Stearyl PG-Trimonium Chloride, Tallowtrimomum Chloride and Undecylenamidopropyltrimonium Methosulfate. 2010. pp.1-6. Unpublished data.

25. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 2009. Washington, DC: FDA.

26. Scientific Committee on Cosmetic Products (SCCP). Opinion on alkyl (C16, C18, C22) trimethylammonium chloride for uses other than as a preservative. 3-17-2006. pp.1-45.

27. McLoughlin D.M., O'Brien J., McManus J.J., Gorelov A.V., and Dawson K.A. A simple and effective separation and purification procedure for DNA fragments using dodecyltrimethylammonium bromide. *Bioseparation*. 2000;9(5):307-313.

28. Mulholland P.J., Self R.L., Harris B.R., Littleton J.M., and Prendergast M.A. Choline exposure reduces potentiation of N-methyl-D-aspartate toxicity by corticosterone in the developing hippocampus. *Brain Res.Dev.Brain Res.* 2004;153(2):203-211.

29. PDR Network.Herbals & Supplements: Choline. http://www.pdrhealth.com/drugs/altmed/altmed-mono.aspx?contentFileName=ame0336.xml&contentName=Choline&contentId=492.

30. PDR Network.Herbals & Supplements: Propionyl-L-carnitine. http://www.pdrhealth.com/drugs/altmed/altmed-mono.aspx?contentFileName=ame0462.xml&contentName=Propionyl-L-carnitine&contentId=617.

31. Herzberg GR, Sheikholislam, B., and Lerner J. Cationic amino acid transport in chicken small intestine. *Comparative Biochemistry and Physiology*. 1971;41A229-247.

32. Herzberg GR and Lerner J. Intestinal absorption of choline in the chick. *Biochemistry and Biophisics Acta*. 1973;307234-242.

33. Kuczler FJ, Nahrwold DL, and Rose RC. Choline influx across the brush border of guinea pig jejunum. *Biochemistry and Biophisics Acta*. 1977;465(131):137.

34. Sheard NF and Zeisel SH. An in vitro study of choline uptake by intestine from neonatal and adult rats. *Pediatric Research*. 1986;20768-722.

35. Politzer Shronts E. Essential nature of choline with implications for total parenteral nutrition. *Journal of the American Diet Association*. 1997;97639-646-649.

36. Zeisel, S. H., Wishnod JS, and Blusztajn JK. Formation of methylamines from ingested choline and lecithin. *Journal of Pharmacology and Experimental Therapeutics*. 1983;225(2):320-324.

37. Le Kim D and Betzing H. Intestinal absorption of polyunsaturated phosphatidycholine in the rat. *Hoppe Seylers Z Physiology Chemistry*. 1976;3571321-1331.

38. Institute of Medicine, National Academy of Sciences USA. Dietary reference intakes for folate, thiamin, niacin, vitamin B12, panthothenic acid, biotin, and choline. Washington, D.C., National Academy Press. 1998. pp. 390-422.

39. Mehta A.K., Arora N., Gaur S.N., and Singh B.P. Acute toxicity assessment of choline by inhalation, intraperitoneal and oral routes in Balb/c mice. *Regul.Toxicol.Pharmacol.* 2009;54(3):282-286.

40. Zeisel SH and Wurtman RJ. Developmental changes in rat blood choline concentration. *Biochemistry Journal*. 1981;198(565):570.

41. Cornford EM and Cornford ME. Nutrient transport and the blood-brain barrier in developing animals. *Federation Proceedings*. 1986;452065-2072.

42. Zeisel SH, Story DL, Wurtman RJ, and Brunengraber H. Uptake of free choline by isolated perfused rat liver. *Proceedings of the National Acadamy of Science USA*. 1980;774417-4419.

43. Acara M and Rest, J. Regulation of plama choline by the renal tubule: Bidirectional transport of choline. *American Journal of Physiology*. 1973;2251123-1128.

44. Rennick B, Acara M, and Glor M. Relations of renal transport rate, transport maximum, and competitor potency for tetraethylammonium and choline. *American Journal of Physiology*. 1977;232(F443):F447.

45. Bianchi G and Azzone GF. Oxidation of choline in rat liver mitochondria. *Journal of Biological Chemistry*. 1964;2393947-3955.

46. Weinhold PA and Sanders R. The oxidation of choline by liver slices and mitochondrea during liver development in the rat. *Life Science*. 1973;13621-629.

47. Kennedy EP and Weiss SB. The function of cytidine coenzymes in the biosynthesis of phospholipids. *Journal of Biological Chemistry*. 1956;222193-214.

48. Vance DE. Boehringer Mannheim Award lecture. Phosphatidylcholine metabolism: Masochistic enzymology, metabolic regulation, and lipoprotein assembly. *Biochemistry and Cell Biology*. 1990;681151-1165.

49. Bremer J and Greenberg D. Methyl transfering enzyme system of microsomes in the biosynthesis of lecithin (phospatidylcholine). *Biochimica et Biophysica Acta*. 1961;46205-216.

50. Vance DE and Ridgway ND. The methylation of phosphatidylethanolamine. *Progress in Lipid Research*. 1988;2761-79.

51. Blusztajn JK, Zeisel SH, and Wurtman RJ. Synthesis of lecithin (phosphatidylcholine) from phosphatidylethanolamine in bovine brain. *Brain Research*. 1979;179319-327.

52. Crews FT, Calderini G, Battistella A, and Toffano G. Age-dependent changes the methylation of rat brain phospholipids. *Brain Research*. 1981;229(256):259.

53. Yang Ek, Blusztajn JK, Pomfret EA, and Zeisel SH. Rat and human mammary tissue can synthesize choline moiety via the methylation of phosphatidylethanolamine. *Biochemistry*. 1988;256821-828.

54. Rebouche CJ. Overview of physiological and pharmacological actions. *Carnitine: The Science Behind a Conditionally Essential Nutrient*. 2004. http://ods.od.nig.gov/News/Carnitine_Conference_Summary.aspx

55. Scientific Committee on Cosmetic Products. Opinion on Alkyl (C16, C18, C22) trimethylammonium chloride: For other uses than as a preservative. 2006. Report No. 0917/05. pp. 1-45.

56. Arch Chemicals, Inc. Material safety data sheet; Quamectant AM-50. 2006. pp.1-8.

57. Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers. Choline chloride. European Commission Enterprise and Industry. 12-9-2003. Date Accessed 4-22-2010. Report No. SCCNFP/0642/03. pp. 1-9.

58. Kim C.S. and Roe C.R. Maternal and fetal tissue distribution of L-carnitine in pregnant mice: low accumulation in the brain. *Fundam.Appl.Toxicol.* 1992;19(2):222-227.

59. Hagen L.E., Berge R.K., and Farstad M. Different subcellular localization of palmitoyl-L-carnitine hydrolysis in human and rat liver. *Febs Lett.* 1979;104(2):297-299.

60. Yoon KA and Burgess DJ. Effect of cationic surfactant on transport of madel drugs in emulsion systems. *Journal of Pharmacy and pharmacology*. 1997;49478-484.

61. Hochman J.H., Fix J.A., and LeCluyse E.L. In vitro and in vivo analysis of the mechanism of absorption enhancement by palmitoylcarnitine. *J.Pharmacol.Exp.Ther.* 1994;269(2):813-822.

62. O'Hagan, D. T., Critchley, H., Farraj, N. F., Fisher, A. N., Johansen, B. R., Davis, S. S., and Illum, L. Nasal absorption enhancers for biosynthetic human growth hormone in rats. *Pharm.Res.%1990.Jul.;7.(7.):772.-6.* (7:772-6).

63. Environmental Protection Agency (EPA). Index of robust summaries: FND Cationics HPV chemicals challenge. Appendix A. 12-13-2001. http://www.epa.gov/chemrtk/pubs/summaries/fatnitro/c13407rs.pdf. Report No. AR201-13407B. pp. 1-237.

64. Cortesi R, Esposito E, Menegatti E, Gambari R, and Nastruzzi C. Effect of cationic liposome composition on in vitro cytotoxicity and protective effect on carried DNA. *International Journal of Pharmaceutics*. 1996;13969-78.

65. Bigliardi, P. L., Herron, M. J., Nelson, R. D., and Dahl, M. V. Effects of detergents on proliferation and metabolism of human keratinocytes. *Exp.Dermatol.%1994.Apr;3(2):89.-94.* (2:89-94).

66. Landsverk, T., Oltedal, E., and Sund, R. B. Studies On Hydragogue Drugs: Light And Electron Microscopic Examination Of The Isolated Rat Colonic Mucosa Exposed To Deoxycholic Acid And Synthetic Surfactants. *Acta Pharmacologica.et Toxicologica.* 1984;54(1).

67. Rodriguez, J. L., Trooskin, S. Z., Greco, R. S., Herbstman, R. A., Donetz, A. P., and Harvey, R. A. Reduced bacterial adherence to surfactant-coated catheters. *Curr.Surg.%1986.Sep.-Oct.;43.(5):423.-5.* (5:423-5).

68. Al-Adham, I. Si, Dinning, A. J., Eastwood, I. M., Austin, P., and Collier, P. J. Cell membrane effects of some common biocides. *Journal of Industrial.Microbiology & Biotechnology*. 1998;21(1-2):6-10.

69. Breen, P. J., Compadre, C. M., Fifer, E. K., Salari, H., Serbus, D. C., and Lattin, D. L. Quaternary ammonium compounds inhibit and reduce the attachment of viable Salmonella typhimurium to poultry tissue. *Journal of Food Science*. 1995;60(6):1191-1196.

70. Ho, I. K., Loh, H. H., and Way, E. L. Toxic interaction between choline and morphine. *Toxicol.Appl.Pharmacol.%1979.Nov.;51.(2):203.-8.* (2:203-8).

71. Agut, J., Font, E., Sacristan, A., and Ortiz, J. A. Dissimilar effects in acute toxicity studies of CDP-choline and choline. *Arzneimittelforschung.%1983.;33.(7A.):1016.-8.* (7A:1016-8).

72. Isomaa B and Bjondahl K. Toxicity and pharmacological properties of surface-active alkyltrimthylammonium bromides in the rat. *Acta Pharmacologica et Toxicoligica*. 1980;4717-23.

73. Cornatzer, W. E. Toxicity of choline and dimethylethanolamine in the guinea pig and the rat. *Proc.Soc.Exp.Biol.Med.%1954.Apr;85.(4):642.-3.* (4:642-3).

74. Gazola, V. A., Lopes, G., Dias, R. M., Curi, R., and Bazotte, R. B. Comparative effects of diet supplementation with l-carnitine and dl-carnitine on ammonia toxicity and hepatic metabolism in rats. *Acta Pharmacol.Sin.%2001.Apr;22.(4):305.-10.* (4:305-10).

75. Sahu, A. P. Effect of choline and mineral fibres (chrysotile asbestos) on guinea-pigs. *Iarc Sci.Publ.%1989.;(90.):185.-9.* (90:185-9).

76. Sahu, A. P., Saxena, A. K., Singh, K. P., and Shanker, R. Effect of chronic choline administration in rats. *Indian J.Exp.Biol.%1986.Feb.;24.(2):91.-6.* (2:91-6).

77. Shivapurkar N, Hoover KL, and Poirier LA. Effect of methionine and choline on liver tumor promotion by phenobarbital and DDT in diethylnitrosamine-initiated rats. *Carcinogenesis*. 1986;7(4):547-550.

78. Muma, N. A., Rowell, P. P., and Schultz, G. S. Effects of long-term dietary choline and phosphatidylcholine administration on muscarinic receptors in aged mouse brain. *Neurol.Res.%1988.Sep.;10(3):130.-5.* (3:130-5).

79. Sahu, A. P., Singh, K. P., Shukla, L. J., and Shanker, R. Choline and mica dust induced pulmonary lesions in rats. *Ind.Health.%1985.;23(2):135.-44.* (2:135-44).

80. Muir, C. K. Surfactant-induced opacity of bovine isolated cornea: an epithelial phenomenon? *Toxicol.Lett.%1987.Sep.;38.(1-2):51.-4.* (1-2:51-4).

81. Gautheron, P., Giroux, J., Cottin, M., Audegond, L., Morilla, A., Mayordomo-Blanco, L., Tortajada, A., Haynes, G., Vericat, J. A., and Et, A. L. Interlaboratory assessment of the bovine corneal opacity and permeability (BCOP) assay. *Toxicology in Vitro*. 1994;8(3):381-392.

82. Vinardell MP, Gonzalez S, and Infante MR. Adaptation of hemoglobin denaturation for assessment of ocular irritation of surfactants and manufactured products. *Journal of Toxicology - Cutaneous and Ocular Toxicology*. 1999;18(4):375-384.

83. Okamoto Y, Ohkoshi K, Itagaki H, Tsuda T, Kakishima H, Ogawa T, Kasai Y, Ohuchi J, Kojima H, Kurishita A, Kaneko T, Matsushima Y, Iwabuchi Y, and Ohno Y. Interlaboratory validation of the *in vitro* eye irritation tests for cosmetic ingredients. (3) Evaluation of the Haemolysis test. *Toxicology in Vitro*. 1999;13115-124.

84. Jester JJ, Li H-F, Petroll M, Parker RD, Cavanagh HD, Carr GJ, Smith, and Maurere JK. Area and depth of surfactant-induced corneal injury correlates with cell death. *Investigative Ophthalmology & Visual Science*. 1998;39(6):922-936.

85. Tani, N., Kinoshita, S., Okamoto, Y., Kotani, M., Itagaki, H., Murakami, N., Sugiura, S., Usami, M., Kato, K., Kojima, H., Ohno, T., Saijo, K., Kato, M., Hayashi, M., and Ohno, Y. Interlaboratory validation of the in vitro eye irritation tests for cosmetic ingredients. (8) Evaluation of cytotoxicity tests on SIRC cells. *Toxicology in Vitro*. 1999;13(1):175-187.

86. Catroux, P., Rougier, A., Dossou, K. G., and Cottin, M. The silicon microphysiometer for testing ocular toxicity in vitro. *Toxicology in Vitro*. 1993;7(4):465-469.

87. Hagino, S., Kinoshita, S., Tani, N., Nakamura, T., Ono, N., Konishi, K., Iimura, H., Kojima, H., and Ohno, Y. Interlaboratory validation of in vitro eye irritation tests for cosmetic ingredients. (2) Chorioallantoic membrane (CAM) test. *Toxicology in Vitro*. 1999;13(1):99-113.

88. Ohno Y, Kaneko T, Kobayashi T, Inoue T, Kuroiwa Y, Yoshida T, Momma J, Hayashi M, Akiyama J, Atsumi T, Chiba K, Endo T, Fujii A, Kakishima H, Kojima H, Masamoto K, Masuda M, Matsukawa S, Ohkoshi K, Okada J, Sakamoto K, Takano K, and Takanaka A. First phase validation of the *in vitro* eye irritation tests for cosmetic ingredients. *In Vitro Toxicology*. 1994;789-94.

89. Okumura, Arashima M, Ohuchi J, Kasai Y, Tsukuma K., Kakishima H, Kotani M, Kojima H, Kurishita A, Hayashi M, Miyajima A, Sunouchi M, and Ohno Y. Interlaboratory validation of the *in vitro* eye irritation tests for cosmetic ingredients. (10) Evaluation of cytotoxicity test on CHL cells. *Toxicology in Vitro*. 1999;13199-208.

90. Tani N, Kinoshita S, Okamoto Y, Kotani M, Itagaki H, Murakami N, Sugiura S, Usami M, Kato K, Kojima H, Ohno T, Saijo K, Kato M, Hayashi M, and Ohno Y. Interlaboratory validation of the *in vitro* eye irritation tests for cosmetic ingredients. (8) Evlauation of cytotoxicity test on SIRC cells. *Toxicology in Vitro*. 1999;13175-187.

91. Matsukawa K, masuda K, Kakishima H, Suzuki K, Nakagawa Y, Matsushige C, Imanishi Y, Nakamura T, Mizutani A, Watanabe R, Shingai T, Kaneko T, Hirose A, and Ohno Y. Interlaboratory validation of the *in vitro* eye irritation tests for cosmetic ingredeints. (11) EYTEX™. *Toxicology in Vitro*. 1999;13209-217.

92. Scientific Committee on Consumer Products. Opinion on choline chloride. United Nations Environment Programme Chemicals Branch. 4-15-2008. Date Accessed 4-22-2010. Report No. SCCP/1159/08. pp. 1-16.

93. Hill Brothers Chemical Co. Material Safety Data Sheet. 2003. pp.1-3.

94. Sanchez, L., Mitjans, M., Infante, M. R., and Vinardell, M. P. Assessment of the potential skin irritation of lysine-derivative anionic surfactants using mouse fibroblasts and human keratinocytes as an alternative to animal testing. *Pharm.Res.* 2004;21(9):1637-41.(9):1637-1641.

95. Larsen ST, Hansen R, Hammer M, Tegner U, Poulsen OM, and Nielsen GD. Adjuvant effect of quaternary ammonium compounds in a murine model. *Toxicology Letters*. 2004;151389-398.

96. Vachhrajani, K. D., Sahu, A. P., and Dutta, K. K. Excess choline availability: a transient effect on spermatogenesis in the rat. *Reprod.Toxicol.%1993.Sep.-Oct.;7.(5):477.-81.* (5:477-81).

97. Davis KL, Bergfeld WF, and Hollister LE. Choline for tardive dyskinesia. *New England Journal of Medicine*. 1975;293152.

98. Zeisel, S. H., da Costa K-A, Franklin PD, Alexander EA, LaMont JT, Sheard NF, and Beiser A. Choline, an essential nutrient for humans. *FASEB*. 1991;52093-2098.

99. Savendahl L, Mar M-H, Underwood LE, and Zeisel SH. Prolonged fasting in humans results in diminished plasma choline concentrations but does not cause liver dysfunction. *American Journal of Clinical Nutrition*. 1997;66222-625.

100. Brass EP. Parmacokinetic considerations for the therapeutic use of carnitine in hemodialysis patients. *Clinical Therapy*. 1995;17176-185.

101. Harper P, Elwin CE, and Cederblad G. Pharmacokinetics of bolus intravenous and oral doses of l-carnitine. *European Journal of Clinical Pharmacology*. 1988;3569-75.

102. Sahajawalla CG, Helton ED, Purich ED, Hoppel CL, and Cabana BE. Multiple-dose pharmacokinetics and bioequivalence of l-carnitine 330-mg tablet versus 1-g chewable tablet versus enteral solution in healthy adult male volunteers. *Journal of Pharmaceutical Sciences*. 1995;84(5):627-633.

103. Krahenbuhl, S. and Reichen, J. Carnitine metabolism in patients with chronic liver disease. *Hepatology.%1997.Jan.;25.(1):148.-53.* (1:148-53).

104. Winter, S., Birek, L., Walker, T., Phalin-Roque, J., Chandler, M. J., Field, C., and Zorn, E. Therapy of metabolic disorders with intravenous (IV) access ports and long term intravenous L-carnitine therapy. *Southeast Asian J.Trop.Med.Public Health.%1999.;30.Suppl 2:152.-3.* 1999.

105. Kwon, O. S. and Chung, Y. B. HPLC determination and pharmacokinetics of endogenous acetyl-L-carnitine (ALC) in human volunteers orally administered a single dose of ALC. *Arch.Pharm.Res.%2004.Jun.;27.(6.):676.-81.* (6:676-81).

106. Wilhelm, K. P., Freitag, G., and Wolff, H. H. Surfactant-induced skin irritation and skin repair: evaluation of a cumulative human irritation model by noninvasive techniques. *J.Am.Acad.Dermatol.%1994.Dec.;31.(6.):981.-7.* (6:981-7).

107. Butler NJ, Langley GR, and Winwood J. A cell suspension agar diffusion test using Neutral Red release to assess the relative irritancy potential of cosmetic ingredients. *International Journal of Cosmetic Science*. 1993;1533-42.

108. Benvenga, S., Ruggeri, R. M., Russo, A., Lapa, D., Campenni, A., and Trimarchi, F. Usefulness of L-carnitine, a naturally occurring peripheral antagonist of thyroid hormone action, in iatrogenic hyperthyroidism: a randomized, double-blind, placebo-controlled clinical trial. *J.Clin.Endocrinol.Metab.%2001.Aug.;86.(8.):3579.-94.* (8:3579-94).

109. Rai, G., Wright, G., Scott, L., Beston, B., Rest, J., and Exton-Smith, A. N. Double-blind, placebo controlled study of acetyl-l-carnitine in patients with Alzheimer's dementia. *Curr.Med.Res.Opin.%1990.;11(10):638.-47.* (10:638-47).

110. Boyd WD, Graham-White J, Blackwood G, Glen I, and McQueen J. Chlincal effects of choline in Alzheimer senile dementia. *Lancet*. 1977;2711.

111. Chawla RK, Wolf DC, Kutner MH, and Bonkovsky HL. Choline may be an essential nutrient in malnourished patients with cirrhosis. *Gastroenterology*. 1989;971514-1520.

112. Davis KL, Hollister LE'Berger PA, and Vento AL. Studies on choline chloride in neuropsychiatric disease: Human and animal data. *Psychopharmacolcogy Bulletin*. 2010;14(4):56-58.

113. Gelenberg AJ, Doller-Wojcik J, and Growdon JH. Choline and lecithine in the treatment of tardive dyskinesia: Prliminary results from a pilot study. *American Journal of Psychiatry*. 1979;136772-776.

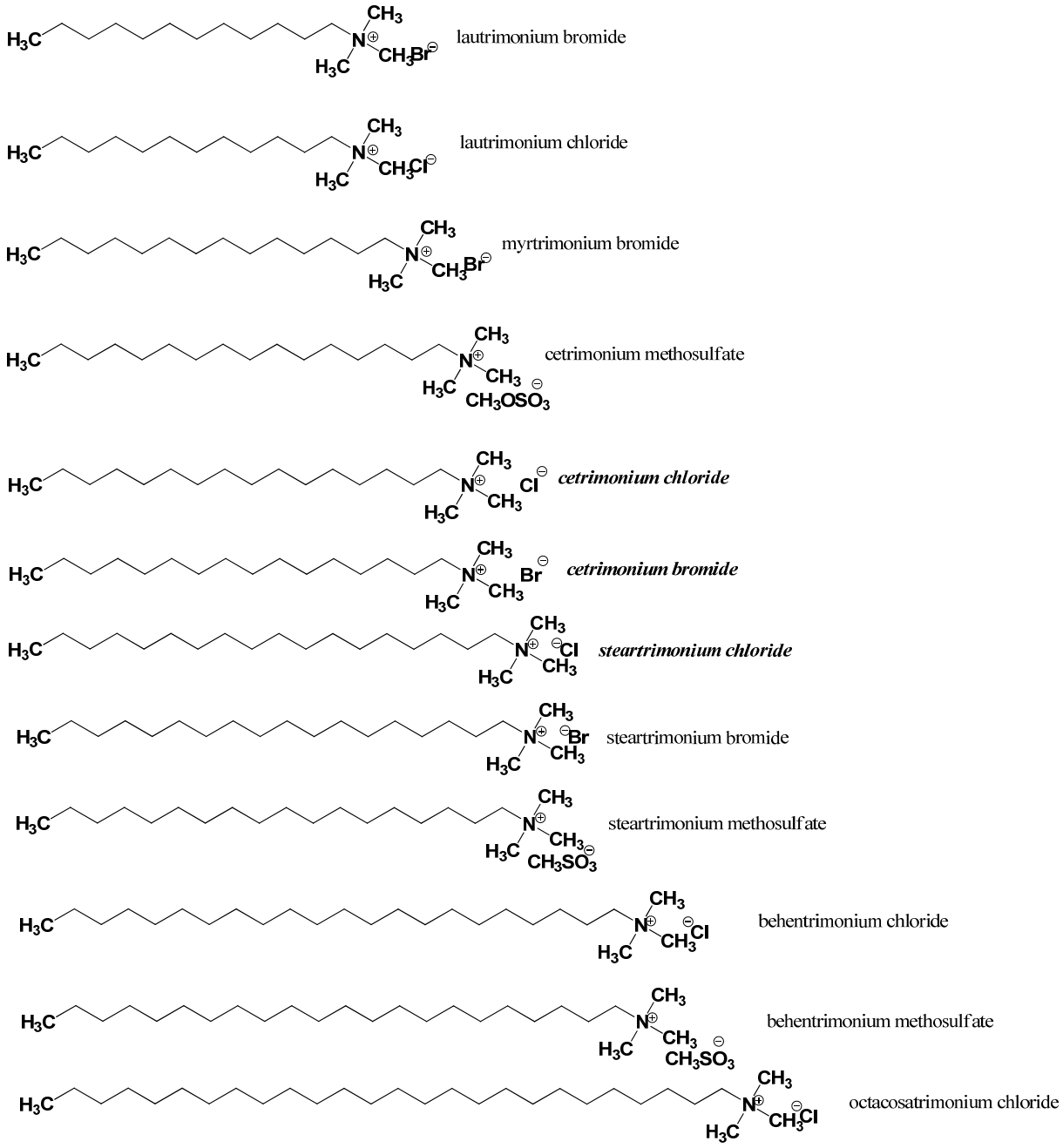
114. Davis KL, Hollister LE'Berger PA, and Vento AL. Studies on choline chloride in neuropsychiatric disease: Human and animal data. *Psychopharmacolcogy Bulletin*. 1978;14(4):56-58.

115. York M, Basketter DA, Cuthbert JA, and Neilson L. Skin irritation testing n man for hazard assessment - evaluation of four patch systems. *Human & Experimental Toxicology*. 1995;14729-734.

116. Basketter DA, Chamberlain M, Griffiths HA, and York M. The classification of skin irritants by human patch test. *Food and Chemical Toxiciology*. 1997;35845-852.

Figure 1a. Structure map of the straight-chain alkyl ingredients in this assessment (including original three assessed

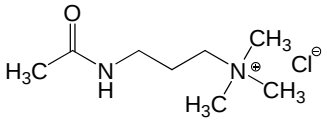
ingredients: *cetrimonium chloride, cetrimonium bromide and steartrimonium bromide,* in bold).



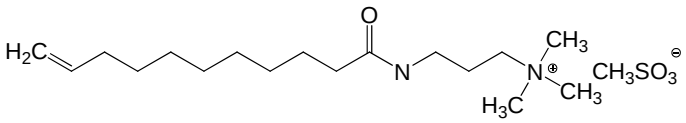
Cocotrimonium chloride, cocotrimonium methosulfate, tallowtrimonium chloride, soytrimonium chloride, hydrogenated palmtrimonium chloride, hydrogenated tallowtrimonium chloride and ceteartrimonium chloride are comprised of mixtures of the above ingredients.

Figure 1b. Structure map of the amide ingredients in this assessment.

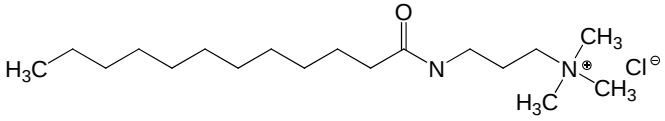
Acetamidopropyl Trimonium Chloride



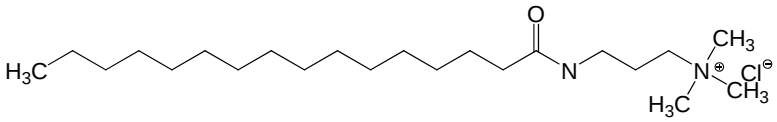
Undecylenamidopropyl Trimonium Methosulfate



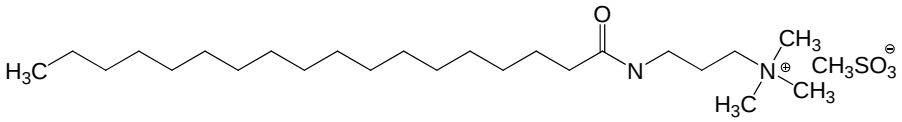
Cinnamidopropyl Trimonium Chloride



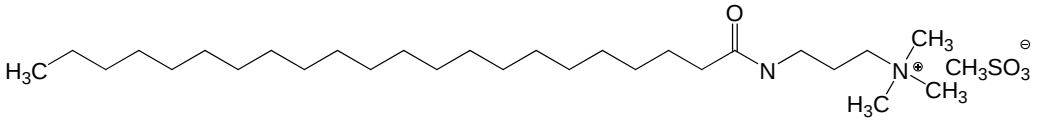
Palmamidopropyl Trimonium Chloride



Stearamidopropyl Trimonium Methosulfate



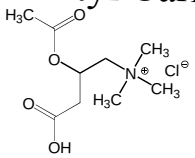
Behenamidopropyl Trimonium Methosulfate



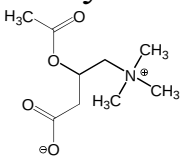
Cocoamidopropyltrimonium chloride, olivamidopropyltrimonium chloride, shea butteramidopropyl trimonium chloride, palmamidopropyl trimonium methosulfate, babassuamidopropyl trimonium chloride and babassuamidopropyl trimonium methosulfate are comprised of mixtures of compounds like those represented above.

Figure 1c. Structure map of the alkanol (choline core structure) ingredients in this assessment.

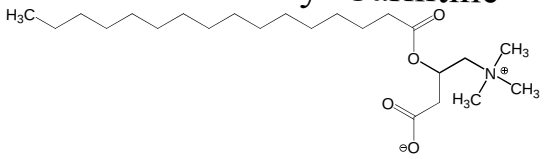
Acetyl Carnitine HCl



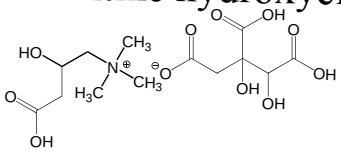
Acetyl Carnitine



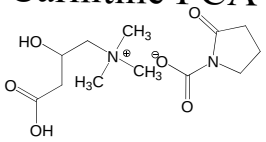
Palmitoyl Carnitine



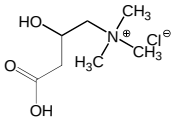
Carnitine hydroxycitrate



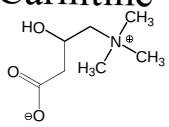
Carnitine PCA



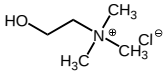
Carnitine HCl



Carnitine

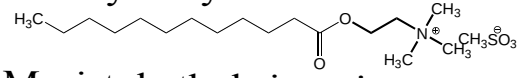


Choline chloride

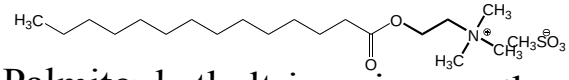


Increasing chain length

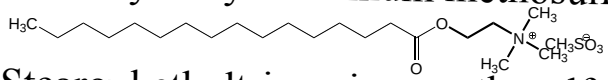
Lauroyl ethyltrimonium methosulfate



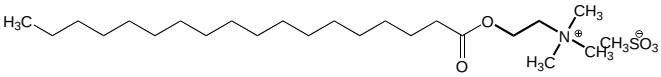
Myristol ethyltrimonium methosulfate



Palmitoyl ethyltrimonium methosulfate



Stearoyl ethyltrimonium methosulfate



Cocoylcholine methosulfate

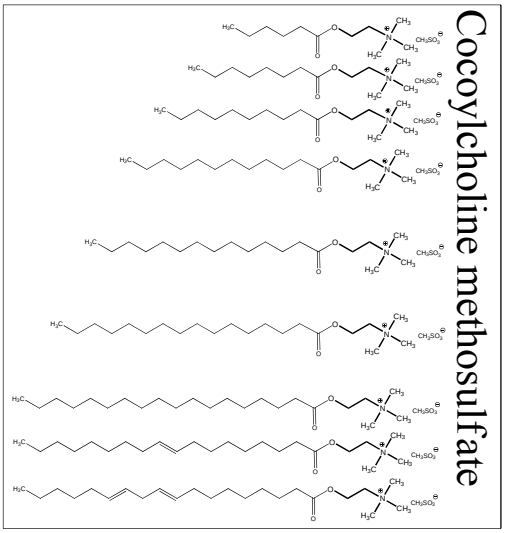
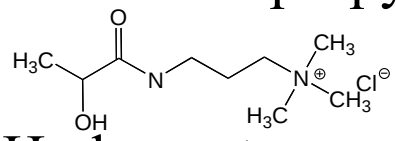
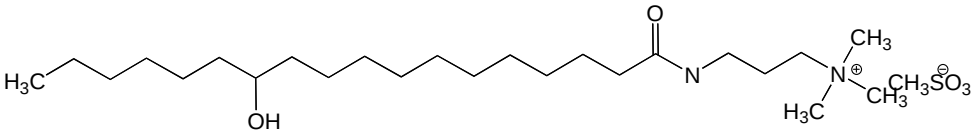


Figure 1d. Structure map of the alkanol amide ingredients in this assessment.

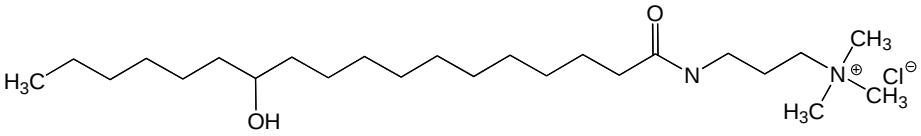
Lactamidopropyl trimonium chloride



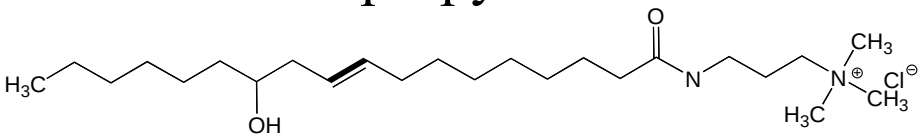
Hydroxystearamido-propyl trimonium methosulfate



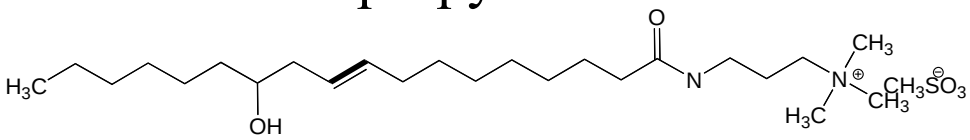
Hydroxystearamido-propyl trimonium chloride



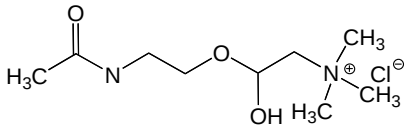
Ricinoleamidepropyl trimonium chloride



Ricinoleamidepropyl trimonium methosulfate



Acetamidoethoxybutyl trimonium chloride



Acetamidoethoxybutyl trimonium chloride

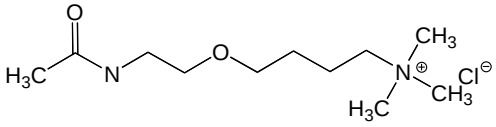
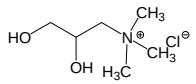


Figure 1e. Structure map of the glycol ingredients in this assessment.

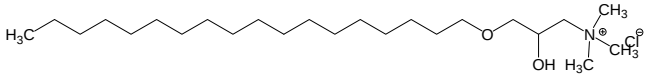
Glycol core

Dihydroxypropyltrimonium chloride

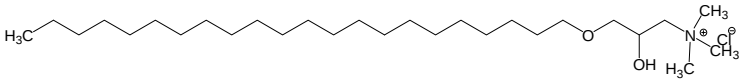


Glycol ethers

Stearyl PG-trimonium chloride

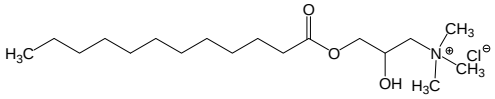


Behenyl PG-trimonium chloride

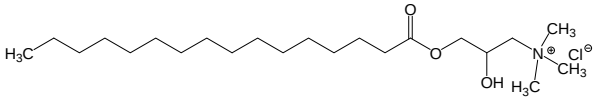


Glycol esters

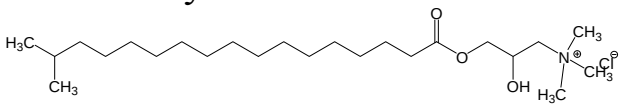
Lauroyl PG-trimonium chloride



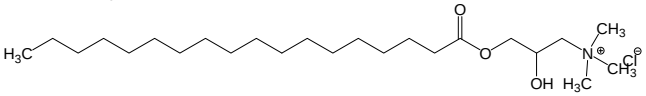
Palmitoyl PG-trimonium chloride



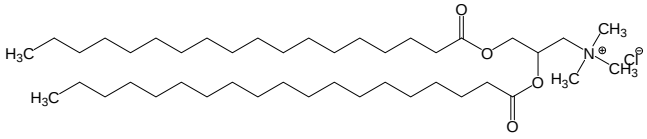
Isostearoyl PG-trimonium chloride



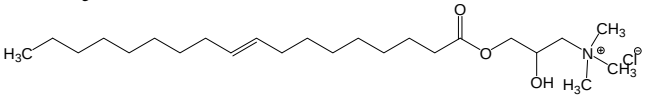
Stearoyl PG-trimonium chloride



Distearoylpropyl trimonium chloride



Oleoyl PG-trimonium chloride



Behenoyl PG-trimonium chloride

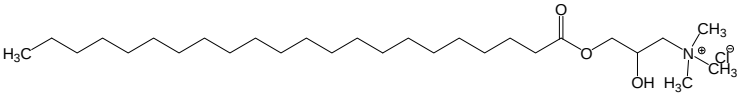


Table 1. Straight-chain alkyl, trimonium compounds and their salts in this safety assessment.

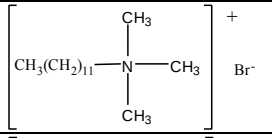
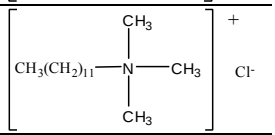
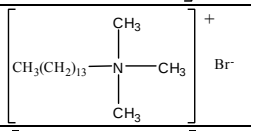
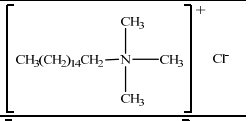
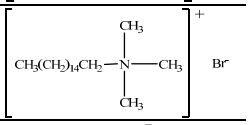
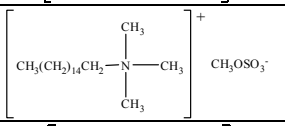
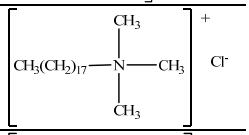
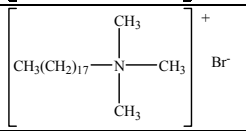
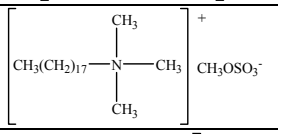
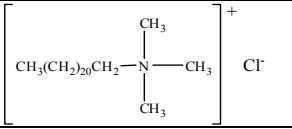
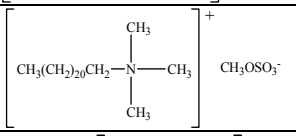
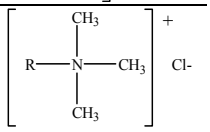
Ingredient	CAS no.	Definition	Function(s)	Formula/structure
Straight-chain alkyl (ingredients from original safety assessment in bold)				
Laurtrimonium bromide	1119-94-4	The quaternary ammonium salt that conforms to the formula in the figure.	Cosmetic biocide; hair conditioning agent	
Laurtrimonium chloride	112-00-5	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agents; cosmetic biocide; emulsifying agent	
Myrtrimonium bromide	1119-97-7	The quaternary ammonium salt that conforms generally to the formula in the figure	Antistatic agents; cosmetic biocide	
Cetrimonium chloride	112-02-7	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; cosmetic biocide; surfactant-emulsifying agent	
Cetrimonium bromide	57-09-0	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; cosmetic biocide; surfactant-emulsifying agent	
Cetrimonium methosulfate	65060-02-8	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; cosmetic biocide; surfactant-emulsifying agent	
Steartrimonium chloride	112-03-8	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Steartrimonium bromide	None	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Steartrimonium methosulfate	18684-11-2	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Behentrimonium chloride	17301-53-0	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Behentrimonium methosulfate	81646-13-1; 241148-21-0	The quaternary ammonium salt that conforms to the formula in the figure	Antistatic Agents; Hair Conditioning Agents	
Octacosatrimonium chloride	None	The quaternary ammonium salt that conforms to the formula in the figure. R represents the octacosanyl (C_{28}) alkyl group.	Antistatic agent; hair conditioning agent	

Table 1. Straight-chain alkyl, trimonium compounds and their salts in this safety assessment.

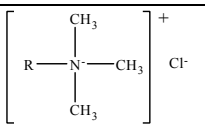
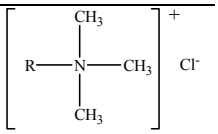
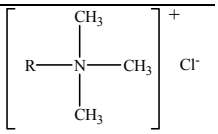
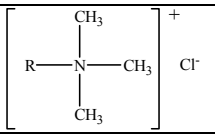
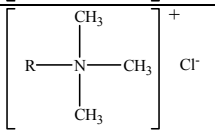
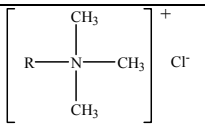
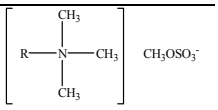
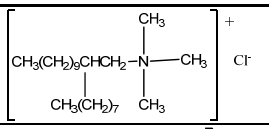
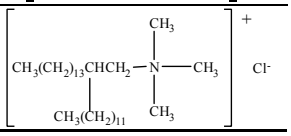
Ingredient	CAS no.	Definition	Function(s)	Formula/structure
Straight-chain alkyl mixtures				
Ceteartrimonium chloride	None	The quaternary ammonium salt that conforms to the formula in the figure. R represents the cetyl and stearyl alkyl groups.	Antistatic agent; hair conditioning agent	
Hydrogenated tallowtrimonium chloride	61788-78-1	The quaternary ammonium salt that conforms generally to the formula in the figure. R represents the alkyl groups derived from hydrogenated tallow.	Antistatic agents; hair conditioning agent	
Hydrogenated palmtrimonium chloride	None	The quaternary ammonium salt that conforms generally to the formula in the figure. R represents the alkyl groups derived from palm oil.	Antistatic agents; hair conditioning agents	
Soytrimonium chloride	61790-41-8	The quaternary ammonium salt that conforms to the formula in the figure. R represents the alkyl groups derived from soy.	Antistatic agent; hair conditioning agent	
Tallowtrimonium chloride	8030-78-2	The quaternary ammonium salt that conforms generally to the formula in the figure. R represents the alkyl groups derived from tallow.	Antistatic agents; hair conditioning agents	
Cocotrimonium chloride	61789-18-2	The quaternary ammonium salt that conforms generally to the formula in the figure. R represents the alkyl groups derived from coconut oil	Antistatic agent; hair conditioning agent	
Cocotrimonium methosulfate	None	The quaternary ammonium salt that conforms generally to the formula in the figure. R represents the alkyl groups derived from coconut oil	Antistatic agent; hair conditioning agent	
Branched alkyl				
Octyldodecyltrimonium chloride	None	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Dodecylhexadecyl-trimonium chloride	103807-18-7	The organic compound that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent; surfactant-emulsifying agent	

Table 2. Amide trimonium compounds and their salts in this safety assessment.

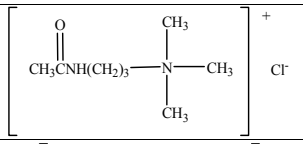
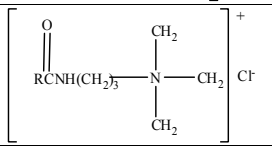
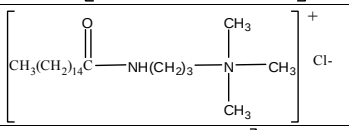
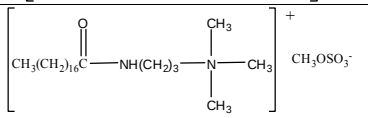
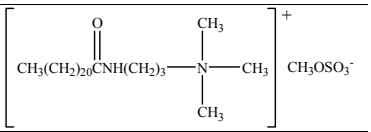
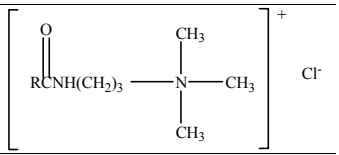
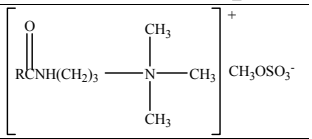
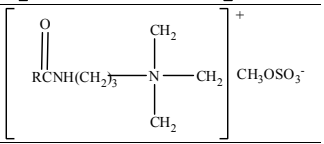
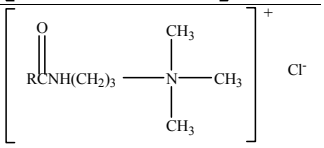
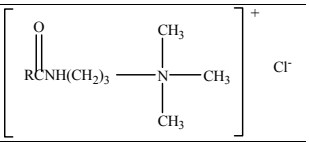
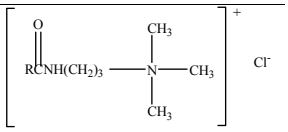
Ingredient	CAS no.	Definition	Function(s)	Formula/structure
Alkyl amidopropyl				
Acetamidopropyl trimonium chloride	123776-56-7	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent	
Cinnamidopropyltrimonium chloride	None	The organic compound that conforms to the formula in the figure. R represents the fatty acids derived from cinnamon oil.	Antistatic agent; hair conditioning agent; light stabilizer	
Palmitamidopropyl trimonium chloride	51277-96-4	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Stearamidoproyl trimonium methosulfate	19277-88-4	The quaternary ammonium salt that conforms generally to the formula in the figure.	Antistatic agent; hair conditioning agent	
Behenamidopropyl-trimonium methosulfate	None	The organic compound that conforms to the formula in the figure.	Hair conditioning agent	
Alkyl amidopropyl mixtures				
Babassuamidopropyl trimonium chloride	None	The quaternary ammonium salt that conforms generally to the formula in the figure. RCO- represents the fatty acids derived from babassu oil.	Antistatic agent; hair conditioning agent; surfactant-emulsifying agent	
Babassuamidopropyl-trimonium methosulfate	None	The quaternary ammonium salt that conforms generally to the formula in the figure. RCO- represents the fatty acids derived from babassu oil.	Antistatic agents; hair conditioning agents; surfactants-emulsifying agent	
Palmamidopropyl trimonium methosulfate	None	The quaternary ammonium salt that conforms to the formula in the figure. RCO- represents the fatty acid moiety derived from palm oil.	Hair conditioning agent	
Shea butteramidopropyl-trimonium chloride	None	The quaternary ammonium salt that conforms generally to the formula in the figure. RCO- represents the fatty acids derived from Butyrospermum Parkii (Shea Butter).	Hair conditioning agents; surfactants-emulsifying agents	
Cocamidopropyltrimonium chloride	None	The quaternary ammonium salt that conforms generally to the formula in the figure. RCO- represents the fatty acids derived from coconut oil	Antistatic agent; hair conditioning agent	
Olivamidopropyltrimonium chloride	None	The quaternary ammonium salt that conforms generally to the formula in the figure. RCO- represents the fatty acids derived from olive oil.	Antistatic agent; hair conditioning agent; surfactant-emulsifying agent	

Table 2. Amide trimonium compounds and their salts in this safety assessment.

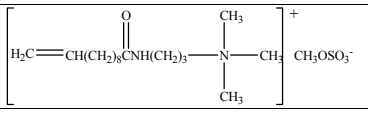
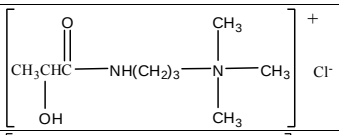
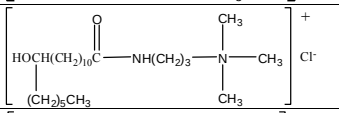
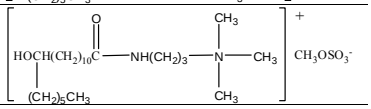
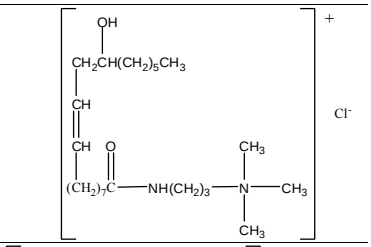
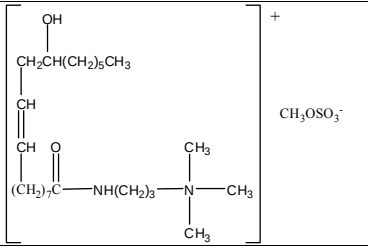
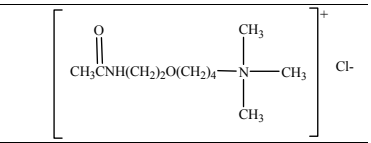
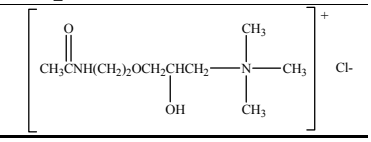
Ingredient	CAS no.	Definition	Function(s)	Formula/structure
Alkenyl amidopropyl				
Undecylenamidopropyl-trimonium methosulfate	None	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Alkanol amidopropyl				
Lactamidopropyl trimonium chloride	93507-51-8	The quaternary ammonium salt that conforms generally to the formula in the figure.	Antistatic agent	
Hydroxystearamidopropyl trimonium chloride	127312-01-0	The organic compound that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Hydroxystearamidopropyl trimonium methosulfate	127312-00-9	The organic compound that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Alkenol amidopropyl				
Ricinoleamidopropyl-trimonium chloride	127311-98-2	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Ricinoleamidopropyl-trimonium methosulfate	85508-38-9	The quaternary ammonium salt that conforms generally to the formula in the figure.	Antistatic agent; hair conditioning agent	
Amido alkyl ether/glycol-ether				
Acetamidoethoxybutyl trimonium chloride	None	The quaternary ammonium salt that conforms to the formula in the figure.	Hair conditioning agent; skin-conditioning agent-miscellaneous	
Acetamidoethyl PG-trimonium chloride	167614-36-0	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	

Table 3. Alkanol trimonium compounds and related ethers/esters/acids in this safety assessment.

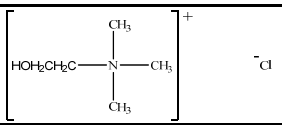
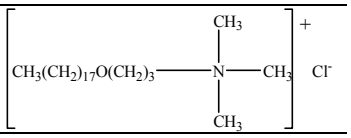
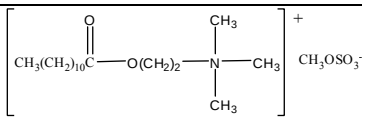
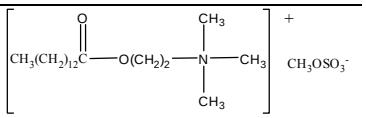
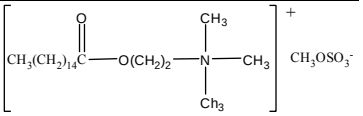
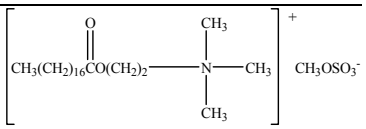
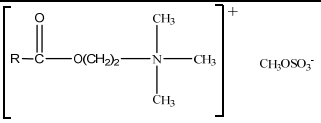
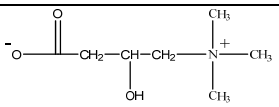
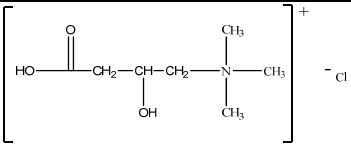
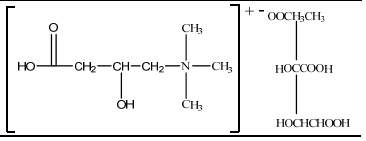
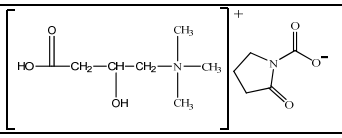
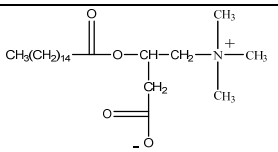
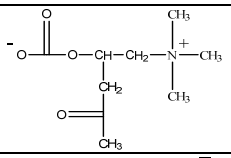
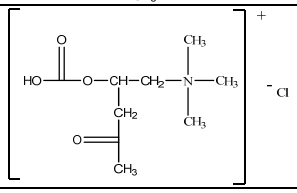
Ingredient	CAS no.	Definition	Function(s)	Formula
Choline Chloride[1]	67-48-1	Choline Chloride is the quaternary ammonium salt that conforms to the formula in the figure.	Skin-Conditioning Agents - Humectant	
Ether				
Stearoxypropyltrimonium chloride	23328-71-4	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; Hair conditioning agent	
Esters				
Lauroyl ethyltrimonium methosulfate	851385-89-2	The quaternary ammonium salt that conforms generally to the formula in the figure.	Surfactant-cleansing agent	
Myristoyl ethyltrimonium methosulfate	851385-90-5	The quaternary ammonium salt that conforms to the formula in the figure.	Surfactant-cleansing agent	
Palmitoyl ethyltrimonium methosulfate	None	The quaternary ammonium salt that conforms to the formula in the figure.	Surfactant-emulsifying agent	
Stearoyl ethyltrimonium methosulfate	None	The quaternary ammonium salt that conforms to the formula in the figure.	Surfactant-emulsifying agent	
Ester mixture				
Cocoylcholine Methosulfate	852690-27-8	Cocoylcholine Methosulfate is the quaternary ammonium salt that conforms generally to the formula, wherein R represents the alkyl groups derived from coconut fatty acid moiety.	Surfactants; Cleansing Agents	
Alkanol acids				
Carnitine	541-15-1	Carnitine is the organic compound that conforms to the formula in the figure.	Antistatic Agents; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous; Surfactants - Cleansing Agents; Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous	
Carnitine HCl	6645-46-1	Carnitine HCl is the organic compound that conforms to the formula in the figure.	Humectants; Skin-Conditioning Agents - Miscellaneous	
Carnitine Hydroxycitrate	None	Carnitine Hydroxycitrate is the organic compound that conforms to the formula in the figure.	Skin-Conditioning Agents - Miscellaneous	

Table 3. Alkanol trimonium compounds and related ethers/esters/acids in this safety assessment.

Ingredient	CAS no.	Definition	Function(s)	Formula
Carnitine PCA	None	Carnitine PCA is the carnitine salt of PCA (q.v.).	Exfoliants	
Acid esters				
Palmitoyl Carnitine	1935-18-8 2364-67-2	Palmitoyl Carnitine is the ester of Carnitine (q.v.) and palmitic acid that conforms to the formula in the figure.	Skin-Conditioning Agents - Miscellaneous	
Acetyl Carnitine	14992-62-2	Acetyl Carnitine is the organic compound that conforms to the formula in the figure.	Skin-Conditioning Agents - Miscellaneous	
Acetyl Carnitine HCl	5080-50-2	Acetyl Carnitine HCl is the organic compound that conforms to the formula in the figure.	Skin-Conditioning Agents - Miscellaneous	

[1] The SCCP[92] concluded that the available data on choline chloride was not sufficient to address concerns about mucous membrane irritation.

Table 4. Glycol trimonium compounds and related ethers/esters in this safety assessment.

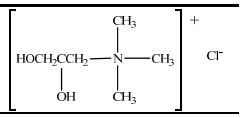
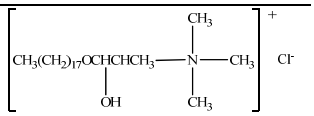
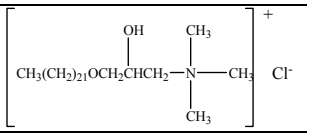
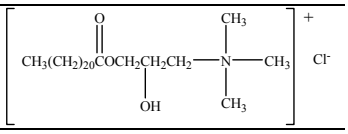
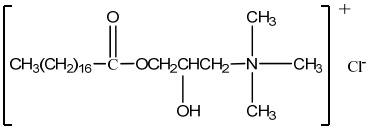
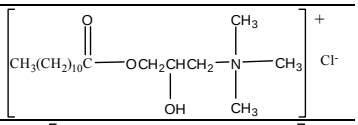
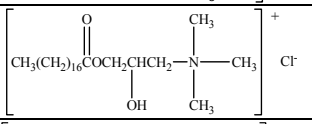
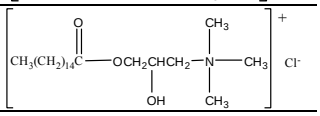
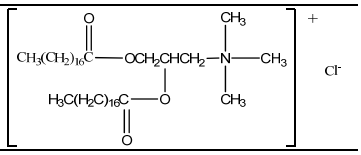
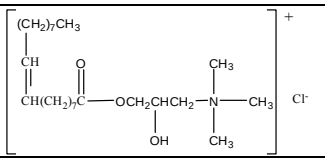
Ingredient	CAS no.	Definition	Function(s)	Formula/structure
Dihydroxypropyltrimonium chloride	34004-36-9	The quaternary ammonium salt that conforms to the formula in the figure	Skin-conditioning agent-humectant	
Ethers				
Stearyl PG-trimonium chloride	None	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agents; hair conditioning agents; surface modifiers; surfactants-emulsifying agents	
Behenyl PG-trimonium chloride	None	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent; surface modifier; surfactant-emulsifying agent	
Esters				
Behenoyl PG-trimonium chloride	69537-38-8	The quaternary ammonium salt that conforms to the figure.	Antistatic agent; hair conditioning agent	
Isostearoyl PG-trimonium chloride	None	The quaternary ammonium salt that conforms generally to the formula in the figure.	Antistatic agent; hair conditioning agent	
Lauroyl PG-trimonium chloride	None	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Stearoyl PG-trimonium chloride	None	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Palmitoyl PG-trimonium chloride	None	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	
Diester				
Distearoylpropyl trimonium chloride	None	The quaternary ammonium salt that conforms generally to the formula in the figure.	Antistatic agents; hair conditioning agent	
Alkenyl ester				
Oleoyl PG-trimonium chloride	None	The quaternary ammonium salt that conforms to the formula in the figure.	Antistatic agent; hair conditioning agent	

Table 5. Polymers containing trimonium in this safety assessment.

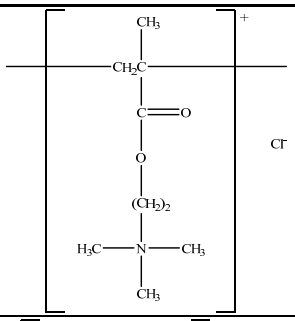
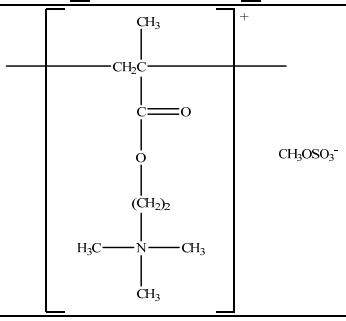
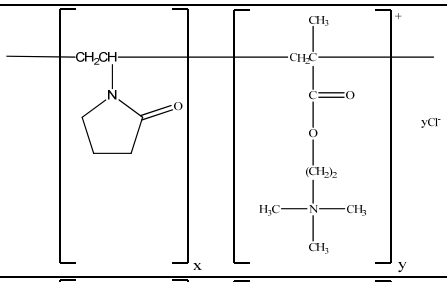
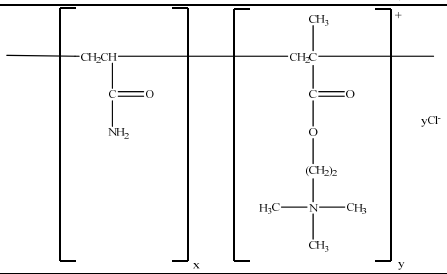
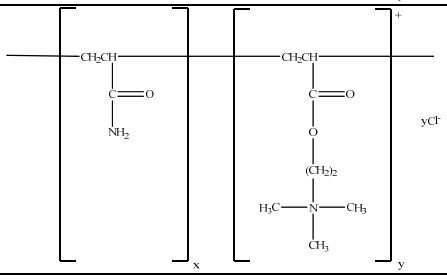
Ingredient	CAS no.	Definition	Function(s)	Formula/structure
Homopolymers				
Polyquaternium-37	26161-33-1	Polyquaternium-37 is the polymeric quaternary ammonium salt that conforms generally to the formula.	Antistatic Agents; Film Formers; Hair Fixatives	
Polyquaternium-14	27103-90-8	Polyquaternium-14 is the polymeric quaternary ammonium salt that conforms generally to the formula.	Antistatic Agents; Film Formers; Hair Fixatives	
Copolymers				
Polyquaternium-28	131954-48-8	Polyquaternium-28 is a polymeric quaternary ammonium salt consisting of vinylpyrrolidone and dimethylaminopropyl methacrylamide monomers. It conforms generally to the formula.	Antistatic Agents; Film Formers; Hair Fixatives	
Polyquaternium-32	35429-19-7	Polyquaternium-32 is the polymeric quaternary ammonium salt that conforms generally to the formula.	Antistatic Agents; Film Formers; Hair Fixatives	
Polyquaternium-33	69418-26-4	Polyquaternium-33 is the polymeric quaternary ammonium salt that conforms generally to the formula.	Antistatic Agents; Film Formers; Hair Fixatives	

Table 5. Polymers containing trimonium in this safety assessment.

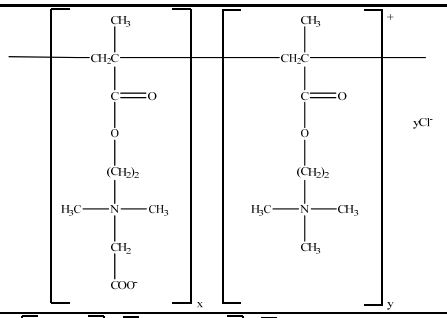
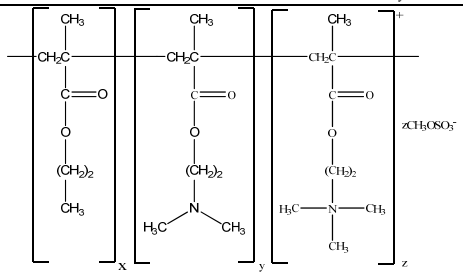
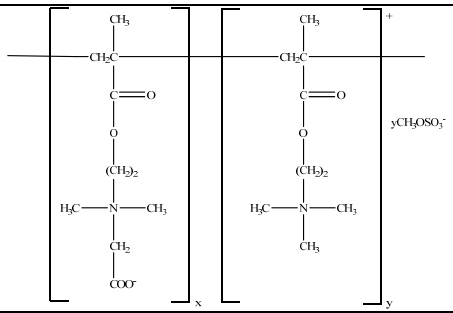
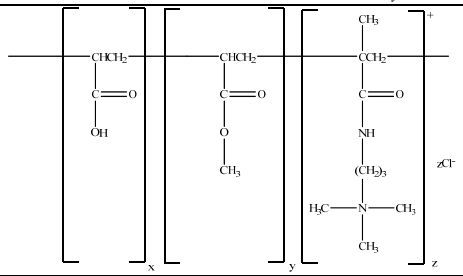
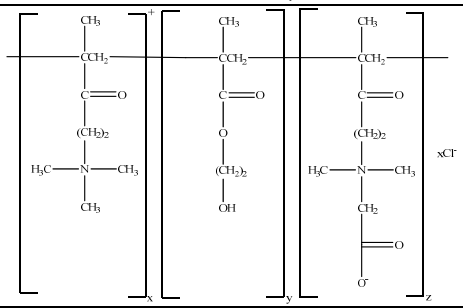
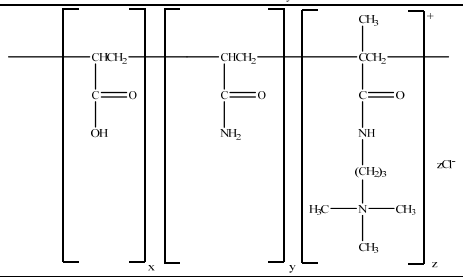
Ingredient	CAS no.	Definition	Function(s)	Formula/structure
Polyquaternium-35	None	Polyquaternium-35 is the polymeric quaternary ammonium salt that conforms generally to the formula.	Antistatic Agents; Film Formers; Hair Fixatives	
Polyquaternium-36	None	Polyquaternium-36 is the polymeric quaternary ammonium salt that conforms generally to the formula.	Antistatic Agents; Film Formers; Hair Fixatives	
Polyquaternium-45	None	Polyquaternium-45 is the polymeric quaternary ammonium salt that conforms generally to the formula.	Antistatic Agents; Film Formers; Hair Fixatives	
Polyquaternium-47	None	Polyquaternium-47 is a polymeric quaternary ammonium chloride formed by the reaction of acrylic acid, methyl acrylate and methacrylamido propyltrimonium chloride.	Film Formers; Hair Fixatives; Skin-Conditioning Agents - Miscellaneous	
Polyquaternium-48	None	Polyquaternium-48 is the polymeric quaternary ammonium salt of formed from methacryloyl ethyl betaine, 2-hydroxyethyl methacrylate and methacryloyl ethyl trimethyl ammonium chloride.	Antistatic Agents; Film Formers; Hair Fixatives	
Polyquaternium-53	84647-38-1	Polyquaternium-53 is the polymeric quaternary ammonium salt formed from acrylic acid, acrylamide and methacrylamidopropyl-trimonium chloride monome.	Hair Conditioning Agents	

Table 5. Polymers containing trimonium in this safety assessment.

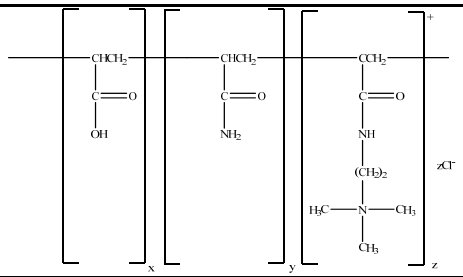
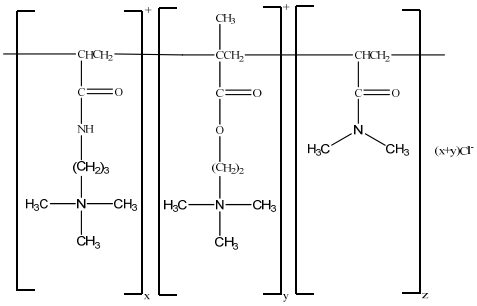
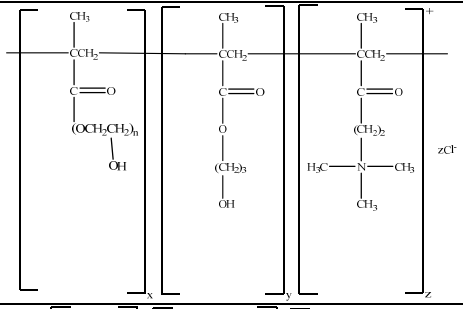
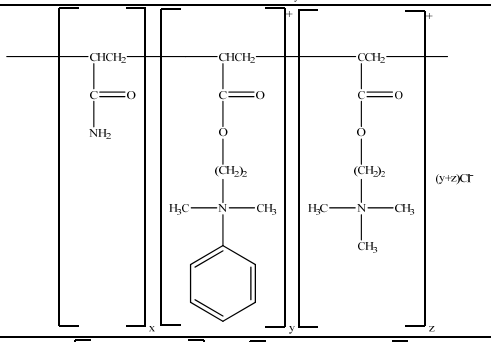
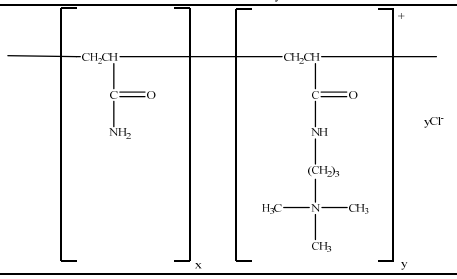
Ingredient	CAS no.	Definition	Function(s)	Formula/structure
Polyquaternium-63	None	Polyquaternium-63 is the polymeric quaternary ammonium salt formed by acrylamide, acrylic acid and ethyltrimonium chloride acrylate.	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous	
Polyquaternium-73	None	Polyquaternium-73 is a polymeric quaternary ammonium salt consisting of propyltrimonium chloride acrylamide, ethyltrimonium chloride methacrylate and dimethylacrylamide monomers.	Antistatic Agents; Film Formers; Hair Conditioning Agents; Hair Fixatives	
Polyquaternium-91	1020103-28-9	Polyquaternium-91 is a polymeric quaternary ammonium salt of hydroxypropyl methacrylate and polyethylene glycol methacrylate quaternized with ethyltrimonium chloride methacrylate.	Film Formers; Hair Conditioning Agents; Surface Modifiers	
Acrylamide/ethyltrimonium chloride acrylate/ethalkonium chloride acrylate copolymer	None	A copolymer of acrylamide, ethyltrimonium chloride acrylate, and ethalkonium chloride acrylate monomers.	Film former, hair conditioning agent; skin-conditioning agent-miscellaneous; slip modifier viscosity increasing agent-aqueous	
Acrylamidopropyl trimonium chloride/acrylamide copolymer	None	A copolymer of acrylamide and acrylamidopropyl-trimonium chloride monomers.	Hair conditioner	

Table 5. Polymers containing trimonium in this safety assessment.

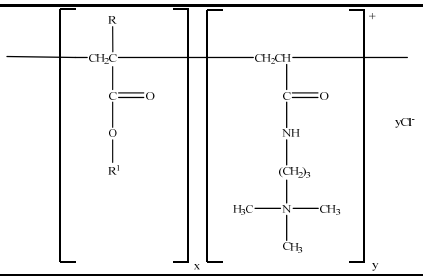
Ingredient	CAS no.	Definition	Function(s)	Formula/structure
Acrylamidopropyl-trimonium chloride/acrylates copolymer	None	A copolymer of one or more of the monomers formed from the amide of acrylic acid, methacrylic acid and aminopropyl-trimethyl-ammonium chloride and one or more monomers of acrylic acid, methacrylic acid or one of their esters.	Antistatic agent; film former; hair fixative	

Table 6. Technical and trade names of straight-chain alkyl, trimonium compounds in this safety assessment.[2]

Ingredient	CAS no.	Technical names	Trade names
Laurtrimonium bromide	1119-94-4	Ammonium, dodecyltrimetyl-,bromide 1-Dodecanaminium, N,N,N-Trimethyl-, Bromide Lauryltrimethylammonium Bromide N,N,N-Trimethyl-1-Dodecanaminiuim Bromide	
Laurtrimonium chloride	112-00-5	Ammonium, Dodecyltrimethyl-, Chloride 1-Dodecanaminium, N,N,N-Trimethyl-, Chloride Dodecyltrimethylammonium Chloride Lauryl Trimethyl Ammonium Chloride N,N,N-Trimethyl-1-Dodecanaminium Chloride	Arquad 12-37W Chemquat 12-33 Chemquat 12-50 Empigen 5089 Laurene Nikkol CA-2150
Myrtrimonium bromide	1119-97-7	Ammonium, Trimethyltertradecyl-, Bromide Myristyl Trimethyl Ammonium Bromide Quaternium-13 1-Tetradecanaminium, N,N,N-Trimethyl-, Bromide Tetradecytrimethylammonium Bromide tetradonium bromide (INN) N,N,N-Trimethyl-1-Tetradecanaminium Bromide	Mytab Rhodaquat M-214C/99 Sumquat 6110
Cetrimonium chloride	112-02-7	Cetyl Trimethyl Ammonium Chloride 1-Hexadecanaminium, N,N,N-Trimethyl-, Chloride Hexadecyltrimethylammonium Chloride N,N,N-Trimethyl-1-Hexadecanaminium Chloride	AEC Cetrimonium Chloride Ammonyx CETAC Ammonyx CETAC-30 Arquad 16-25W Arquad 16-29W Barquat CT-29 Carsoquat CT-429 CTAC Dehyquart A-CA Genamin CTAC Genamin CTAC 50 Incroquat CTC-30 Jeequat CT-29 Nikkol CA-2330 Nikkol CA-2350 OriStar CMC Protaquat CT-29 Saboquat CTA Saboquat CTA 25 Thorquat CTC30 Varisoft 300
Cetrimonium bromide	57-09-0	Cetab cetrimidum (EP) cetrimonium bromide (INN) Cetyl Trimethyl Ammonium Bromide Cetyltrimethylammonium Bromide Powder 1-Hexadecanaminium, N,N,N-Trimethyl-, Bromide Hexadecyltrimethylamine Bromide Hexadecyltrimethylammonium Bromide N,N,N-Trimethyl-1-Hexadecanaminium Bromide	Acetoquat CTAB Bromat Cetrimide Rhodaquat M-242B/99 RonaCare Cetrimonium Bromide RonaCare Cetrimonium Bromide Sumquat 6030
Cetrimonium methosulfate	65060-02-8	Cetyltrimethylammonium Methyl Sulfate 1-Hexadecanaminium, N,N,N-Trimethyl-, Methyl Sulfate Hexadecyltrimethylammonium Methosulfate N,N,N-Trimethyl-1-Hexadecanaminium Methyl Sulfate	Crodazosoft DBQ
Cetrimonium saccharinate	2478-29-7	Cetyltrimethylammonium Benzosulfimide Cetyltrimethylammonium Saccharinate Solution 1-Hexadecanaminium, N,N,N-Trimethyl-, Salt with 1,2-Benzisothiazol-3(2H)-one, 1,1-Dioxide (1:1)	
Cetrimonium tosylate	138-32-9	Cetyl Trimethyl Ammonium p-Toluene Sulfonate; 1-Hexadecanaminium, N,N,N-Trimethyl-, Salt with 4-Methylbenzenesulfonic Acid (1:1); Hexadecyltrimethylammonium p-Tosylate; N,N,N-Trimethyl-1-Hexadecanaminium Salt with 4-Methylbenzenesulfonic Acid	Cetats

Table 6. Technical and trade names of straight-chain alkyl, trimonium compounds in this safety assessment.[2]

Ingredient	CAS no.	Technical names	Trade names
Steartrimonium chloride	112-03-8	1-Octadecanaminium, N,N,N-Trimethyl-, Chloride; Quaternium-10; Stearyl Trimethyl Ammonium Chloride; Stearyl Trimethyl Ammonium Chloride Solution; N,N,N-Trimethyl-1-Octadecanaminium Chloride	Genamin STAC Nikkol CA-2450 Nikkol CA-2465 OriStar STAC
Steartrimonium bromide	None		
Steartrimonium methosulfate	18684-11-2	1-Octadecanaminium, N,N,N-Trimethyl-, Methyl Sulfate; Stearyl Trimethylammonium Methyl Sulfate; Stearyltrimonium Methosulfate; N,N,N-Trimethyl-1-Octadecanaminium Methyl Sulfate	Empigen CM
Steartrimonium saccharinate	None		
Behentrimonium chloride	17301-53-0	1-Docosanaminium, N,N,N-Trimethyl-, Chloride; N,N,N-Trimethyl-1-Docosanaminium Chloride	Genamin BTLF; Genamin KDMP; Incroquat Behenyl TMC-85; Nikkol CA-2580; Varisoft BT 85 Pellets
Behentrimonium methosulfate	81646-13-1; 241148-21-0	Behenyl Trimethyl Ammonium Methosulfate; 1-Docosanaminium, N,N,N-Trimethyl-, Methosulfate; N,N,N-Trimethyl-1-Docosanaminium Methosulfate	Global Seven Gloquat BQ Incroquat Behenyl 18-MEA Incroquat Behenyl TMS Incroquat Behenyl TMS Incroquat Behenyl TMS-50 KeraTint EZ Varisoft BTMS Pellets
Octacosatrimonium chloride	None	Alkyl (28) Trimethyl Ammonium Chloride	
Straight-chain alkyl mixtures			
Ceteartrimonium chloride	None	Alkyl (16,18) Trimethylammonium Chloride	
Hydrogenated tallowtrimonium chloride	61788-78-1	Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Trimethyl, Chlorides	Arquad HT-50
Hydrogenated palmtrimonium chloride	None		
Soytrimonium chloride	61790-41-8	Quaternary Ammonium Compounds, Trimethylsoy Alkyl, Chlorides; Quaternium-9; N-(Soy Alkyl)-N,N,N-Trimethyl Ammonium Chloride; Soyatrimonium Chloride; Soy Trimethyl Ammonium Chloride	Arquad S-60 PG Silab'Capilisse
Tallowtrimonium chloride	8030-78-2	Quaternary Ammonium Compounds, Tallow Alkyl Trimethyl, Chlorides; Tallow Trimethyl Ammonium Chloride	ACC AMD-2 Emulsion Arquad T-50 Dow Corning 1669 Cationic Emulsion Emulsil CT-30 Jeesilc 92
Cocotrimonium chloride	61789-18-2	The quaternary ammonium salt that conforms generally to the formula in the figure. R represents the alkyl groups derived from coconut oil	Antistatic agent; hair conditioning agent
Cocotrimonium methosulfate	None		Luviquat Mono LS; Servamine KAC 458
Branched alkyl			
Octyldodecyltrimonium chloride	None		
Dodecylhexadecyl-trimonium chloride	103807-18-7	1-Hexadecanaminium, 2-Dodecyl-N,N,N-Trimethyl-, Chloride	Quartamin 280GP

Table 7. Technical and trade names of amide trimonium compounds in this safety assessment.[2]

Ingredient	CAS no.	Technical names	Trade names
Alkyl amidopropyl			
Acetamidopropyl trimonium chloride	123776-56-7	3-(Acetylamino)-N,N,N-Trimethyl-1-Propanaminium Chloride; 1-Propanaminium, 3-(Acetylamino)-N,N,N-Trimethyl-, Chloride	AEC Acetamidopropyl Trimonium Chloride; Incromectant AQ; Quamide AME-50
Cinnamidopropyltrimonium chloride	None		Crodasorb UV-283
Palmitamidopropyl trimonium chloride	51277-96-4	(Hexadecylamidopropyl)trimethylammonium Chloride; 1-Propanaminium, N,N,N-Trimethyl-3-((1-oxohexadecyl)amino)-, Chloride; Trimethyl(3-Palmitamidopropyl)Ammonium Chloride	Varisoft PATC
Stearamidoproyl trimonium methosulfate	19277-88-4	1-Propanaminium, N,N,N-Trimethyl-3-[(1-Oxooctadecyl)Amino]-, Methyl Sulfate; N,N,N-Trimethyl-3-[(1-Oxooctadecyl)Amino]-1-Propanaminium Methyl Sulfate	
Behenamidopropyl-trimonium methosulfate	None		Incroquat BBO-35
Alkyl amidopropyl mixtures			
Babassuamidopropyl-trimonium chloride	None		Polygreen Orbignya Quat
Babassuamidopropyl-trimonium methosulfate	None		Incroquat BBO-35
Palmamidopropyl trimonium methosulfate	None		
Shea butteramidopropyl-trimonium chloride	None		Lipex Shea Q
Cocamidopropyltrimonium chloride	None		
Olivamidopropyltrimonium chloride	None		Polygreen Catiolive
Alkenyl amidopropyl			
Undecylenamidopropyl-trimonium methosulfate	None	Undecylenamidopropyl Trimethylammonium Methyl Sulfate	Rewocid UTM 185
Alkanol amidopropyl			
Lactamidopropyl trimonium chloride	93507-51-8	3-Lactamidopropyl)Trimethylammonium Chloride; 1-Propanaminium, 3-((2-hydroxy-1-oxopropyl)amino)-N,N,N-trimethyl-, chloride	AEC Lactamidopropyl Trimonium Chloride; Incromectant LQ
Hydroxystearamidopropyl trimonium chloride	127312-01-0	3-[(12-Hydroxy-1-Oxooctadecyl)Amino]-N,N,N-Trimethyl-1-Propanaminium Chloride; 1-Propanaminium, 3-[(12-Hydroxy-1-Oxooctadecyl)Amino]-N,N,N-Trimethyl-, Chloride	
Hydroxystearamidopropyl trimonium methosulfate	127312-00-9	3-[(12-Hydroxy-1-Oxooctadecyl)Amino]-N,N,N-Trimethyl-1-Propanaminium Methyl Sulfate (Salt); 1-Propanaminium, 3-[(12-Hydroxy-1-Oxooctadecyl)Amino]-N,N,N-Trimethyl-, Methyl Sulfate (Salt)	
Alkenol amidopropyl			
Ricinoleamidopropyl-trimonium chloride	127311-98-2	3-[(12-Hydroxy-1-Oxo-9-Octadecenyl)Amino]-N,N,N-Trimethyl-2-Propanaminium Chloride; 1-Propanaminium, 3-[(12-Hydroxy-1-Oxo-9-Octadecenyl)Amino]-N,N,N-Trimethyl-, Chloride; Ricinoleamidopropyl Trimethylammonium Chloride	
Ricinoleamidopropyl-trimonium methosulfate	85508-38-9	3-[(12-Hydroxy-1-Oxo-9-Octadecenyl)Amino]-N,N,N-Trimethyl-1-Propanaminium Methyl Sulfate; 1-Propanaminium, 3-[(12-Hydroxy-1-Oxo-9-Octadecenyl)Amino]-N,N,N-Trimethyl-, Methyl Sulfate; Ricinoleamidopropyl Trimethylammonium Methyl Sulfate	Varisoft RTM 50
Amido alkyl ether/glycol-ether			
Acetamidoethoxybutyl trimonium chloride	None		
Acetamidoethyl PG-trimonium chloride	167614-36-0	1-Propanaminium, 3-[2-(Acetylamino)Ethoxy]-2-Hydroxy-N,N,N-Trimethyl-, Chloride	AC Quaternized Acetamide; Quamectant AM-50

Table 8. Technical and trade names of alkanol trimonium compounds in this safety assessment.[2]

Ingredient	CAS no.	Technical names	Trade names
Choline chloride	67-48-1	Choline chloride (INN); Ethanaminium, 2-Hydroxy-N,N,N-Trimethyl-, Chloride; Ethannaminium, 2-Hydroxy-N,N,N-Trimethyl, Chloride; (β-Hydroxyethyl)Trimethylammonium Chloride	Choline Chloride Aqueous Solution
Ether			
Stearoxypropyltrimonium chloride	23328-71-4	Ammonium, Trimethyl[3-Octadecyloxy)Propyl]-, Chloride	Quartamin E-80K
Esters			
Lauroyl ethyltrimonium methosulfate	851385-89-2		Surfactive V 12
Myristoyl ethyltrimonium methosulfate	851385-90-5		Surfactive V 14
Palmitoyl ethyltrimonium methosulfate	None		Surfactive V 16
Stearoyl ethyltrimonium methosulfate	None		Surfactive V 18
Ester mixture			
Cocoylcholine Methosulfate	852690-27-8	Ethanaminium, 2-Hydroxy-N,N,N-Trimethyl-, Esters with Coco Fatty Acids, Me Sulfates	surfactive vcc
Alkanol acids			
Carnitine	541-15-1	Ammonium, (3-carboxy-2-hydroxypropyl)trimethyl-, hydroxide, inner salt, L-; 3-Carboxy-2-Hydroxy-N,N,N-Trimethyl-1-PropanaminiumHydroxide, Inner Salt; carnitine (INN); levocarnitine (INN); 1-Propanaminium, 3-Carboxy-2-Hydroxy-N,N,N-Trimethyl-, Hydroxide, Inner Salt	AEC Carnitine (Acetyl L); Natrulon RC Reparative/Exfoliant; Natrulon RC-50 Reparative/Exfoliant; OriStar LCNT
Carnitine HCl	6645-46-1	DL-Carnitine HCl; L-Carnitine Hydrochloride; 1-Propanaminium, 3-Carboxy-1-, Hydroxyl-N,N,N-Trimethyl-, Chloride; 1-Propanaminium, 3-Carboxy-2-Hydroxy-N,N,N-Trimethyl-, Chloride	OriStar LCH; Seltzer Chemicals L-Carnitine HCL
Carnitine Hydroxycitrate	None		Lipolyse HCC
Carnitine PCA	None		Vamactive CR
Acid esters			
Palmitoyl Carnitine	1935-18-8; 2364-67-2	Ammonium, (3-Carboxy-2-Hydroxypropyl)trimethyl-, Hydroxide, Inner Salt, Palmitate; Hexadecanoyl Carnitine; Palmitic Acid, Ester with (3-Carboxy-2-Hydroxypropyl)Trimethylammonium Hydroxide Inner Salt; Propanaminium, 3-Carboxy-N,N,N-Trimethyl-2-((1-Oxohexadecyl)Oxy)-, Inner Salt	Vexel
Acetyl Carnitine	14992-62-2	1-Propanaminium, 2-(Acetyloxy)-3-Carboxy-N,N,N-Trimethyl-, Inner Salt	OriStar ACC
Acetyl Carnitine HCl	5080-50-2	1-Propanaminium, 2-(Acetyloxy)-3-Carboxy-N,N,N-Trimethyl-, Chloride	Acetyl-L-Carnitine Hydrochloride; OriStar ACH

Table 9. Technical and trade names of glycol trimonium compounds in this safety assessment.[2]

Ingredient	CAS no.	Technical names	Trade names
Dihydroxypropyltrimonium chloride	34004-36-9		PD Quat
Ethers			
Stearyl PG-trimonium chloride	None		atinal SHC-65ET
Behenyl PG-trimonium chloride	None		Catinal BHC-60BE
Esters			
Behenoyl PG-trimonium chloride	69537-38-8	(3-Behenoyloxy-2-Hydroxypropyl)Trimethyl Ammonium Chloride	Quartamin BTC 131
Isostearoyl PG-trimonium chloride	None		
Lauroyl PG-trimonium chloride	None		Quartamin BTC 132
Stearoyl PG-trimonium chloride	None	Stearoyl Propylene Glycol Trimethylammonium Chloride	
Palmitoyl PG-trimonium chloride	None		
Diester			
Distearoylpropyl trimonium chloride	None		
Alkenyl ester			
Oleoyl PG-trimonium chloride	None		

Table 10. Technical and trade names of polymers containing trimonium in this safety assessment.[2]

Ingredient	CAS no.	Technical names	Trade names
Homopolymers			
Polyquaternium-37	26161-33-1	Choline, Chloride, Methacrylate, Polymer; Ethanaminium, N,N,N-Trimethyl-2-[(Methyl-1-Oxo-2-Propenyl)Oxy]-, Chloride, Homopolymer; Trimethylaminoethyl Methacrylate Chloride Polymer; N,N,N-Trimethyl-2-[(Methyl-1-Oxo-2-Propenyl)Oxy]Ethanaminium Chloride, Homopolymer	Kleasol 100XT; OriStar PQ37; Synthalen CN; Synthalen CR; Synthalen CU; Syntran PC 5320; Ultragel 300
Polyquaternium-14	27103-90-8	Choline, Methyl Sulfate, Methacrylate, Polymer; Ethanaminium, N,N,N-Trimethyl-2-[(2-Methyl-1-Oxo-2-Propenyl)Oxy]-, Methyl Sulfate, Homopolymer	
Copolymers			
Polyquaternium-28	131954-48-8	* 1-Propanaminium, N,N,N-Trimethyl-3-((2-Methyl-1-Oxo-2-Propenyl)Amino)-, Chloride, Polymer with 1-Ethenyl-2-Pyrrolidinone; Vinylpyrrolidone/Methacrylamidopropyltrimethylammonium Chloride Copolymer	1-Propanaminium, N,N,N-Trimethyl-3-((2-Methyl-1-Oxo-2-Propenyl)Amino)-, Chloride, Polymer with 1-Ethenyl-2-Pyrrolidinone; Vinylpyrrolidone/Methacrylamidopropyltrimethylammonium Chloride Copolymer
Polyquaternium-32	35429-19-7	Acrylamide-Dimethylaminoethyl Methacrylate Methyl Chloride Copolymer; Ethanaminium, N,N,N-Trimethyl-2-[(2-Methyl-1-Oxo-2-Propenyl)Oxy]-, Chloride, Polymer with 2-Propenamide * Acrylamide-Dimethylaminoethyl Methacrylate Methyl Chloride Copolymer; Ethanaminium, N,N,N-Trimethyl-2-[(2-Methyl-1-Oxo-2-Propenyl)Oxy]-, Chloride, Polymer with 2-Propenamide	
Polyquaternium-33	69418-26-4	Acrylamide-Dimethylaminoethyl; Ethanaminium, N,N,N-Trimethyl-2-[1-Oxo-2-Propenyl)Oxy]-, Chloride, Polymer with 2-Propenamide.	Ultimer CG-200
Polyquaternium-35	None		Plex 3074 L
Polyquaternium-36	None		Plex 4739 L
Polyquaternium-45	None		
Polyquaternium-47	None	1-Propanaminium, N,N,N-Trimethyl-3-((2-Methyl-1-Oxo-2-Propenyl)Amino)-, Chloride, Polymer with Methyl 2-Propenoate and 2-Propenoic Acid	Merquat 2001; Merquat 2001N
Polyquaternium-48	None		Plascize L-450
Polyquaternium-53	84647-38-1	Acrylic Acid/Acrylamide/Methacrylamidopropyltrimonium Chloride Copolymer	Merquat 2003
Polyquaternium-63	None		Octacare PQ63; OF-308
Polyquaternium-73	None		Diaformer C-802; Diaformer C-823; Diasleek C-802; Diasleek C-823
Polyquaternium-91	1020103-28-9	Ethanaminium, N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propeny-1-yl)oxy]-, chloride (1:1), polymer with α-(1-oxo-2-propen-1-yl)-θ-hydroxypoly(oxy-1,2-ethanediyl) and 1,2-propanediol mono(2-methyl-2-propenoate)	Film Formers; Hair Conditioning Agents; Surface Modifiers
Acrylamide/ethyltrimonium chloride acrylate/ethalkonium chloride acrylate copolymer	None		Ultimer CG-400
Acrylamidopropyltrimonium Chloride/Acrylamide Copolymer	None		Salcare SC60
Acrylamidopropyl-trimonium chloride/acrylates copolymer	None		Produkt W 37194

Table 11. Physical and chemical properties

Property	Value
Straight-chain alkyl	
Behentrimonium chloride	
Molecular weight	404.161
Appearance	Waxy solid (mixed with isopropanol) White solid (mixed with cetearyl alcohol)
Odor	Similar of isopropanol (mixed with isopropanol)
Melting Point (ºC)	85 (mixed with isopropanol) ~50 (mixed with cetaryl alcohol)
pH	4.9 (3% in water; mixed with isopropanol) 6.0-7.5 (10% in water; mixed with cetaryl alcohol)
Density (kg/m^3)	900
Behentrimonium methosulfate	
Molecular weight	479.801
Cetrimonium bromide	
Molecular weight	364.48
Melting point (ºC)	237-243
Solubility	Water and acetone Not in benzene and ether
pH	Stable in acidic pH Opimum biocide range 4-10
Incompatible	anionics, soap, nitrates, heavy metals, oxidants, rubber, proteins, and blood
Cetrimonium chloride	
Stabilibty (2% in mineral oil/water emulsion)	5, 25, 37, and 60°C for 1 month
Cetrimonium methosulfate	
Molecular weight	395.640
Cetrimonium saccharinate	
Molecular weight	466.721
Cetrimonium tosylate	
Molecular weight	455.74
Laurtrimonium bromide	
Molecular weight	308.346
Melting point (ºC)	293 (in acetone) 243 217-219 (in ethanol, diethyl ether) 228-230 231 218-220 245 61 246
Laurtrimonium chloride	
Molecular weight	263.895
Melting point (ºC)	246 248-249.5 (in ethyl acetate)
Solubility	Carbon tetrachloride, chloroform
Laurtrimonium trichlorphenoxide	
Molecular weight	424.88
Myrtrimonium bromide	
Molecular weight	350.42
Appearance	Amber liquid
Odor	Characteristic
pH	7.5-8.5
Boiling point (ºC)	100
Density	1
Steartrimonium bromide	
Molecular weight	392.50
Steartrimonium chloride	
Molecular weight	348.13
Appearance	Amber liquid
Active quaternary (%)	~50
Steartrimonium methosulfate	
Molecular weight	423.69

Table 11. Physical and chemical properties

Property	Value
Steartrimonium saccharinate	
Molecular weight	494.77
Straight-chain alkyl mixtures	
Soytrimonium Chloride	
pH	7.5-8.5
Odor	Characteristic
Boiling Point	100º
Tallowtrimonium chloride	
Appearance	Clear to pale yellow liquid
Boiling point (ºC)	100
Melting point (ºC)	20
pH	6-9 (10% aqueous)
Solubility	water
Branched alkyl	
Dodecylhexadecyl-trimonium chloride	
Molecular weight	488.322
Octyldodecyltrimonium chloride	
Molecular weight	376.108
Alkyl amidopropyl	
Acetamidopropyl trimonium chloride	
Molecular weight	194.704
Behenamidopropyltrimonium methosulfate	
Molecular weight	550.879
Palmitamidopropyltrimonium chloride	
Molecular weight	391.079
Stearamidoproyl trimonium methosulfate	
Molecular weight	494.772
Alkenyl amidopropyl	
Undecylenamidopropyltrimonium methosulfate	
Molecular weight	394.569
Alkanol amidopropyl	
Lactamidopropyl trimonium chloride	
Molecular weight	224.730
Hydroxystearamidopropyl trimonium chloride	
Molecular weight	435.132
Hydroxystearamidopropyl trimonium methosulfate	
Molecular weight	510.771
Alkenol amidopropyl	
Ricinoleamidopropyltrimonium chloride	
Molecular weight	433.166
Appearance	Slightly viscous liquid
pH	3.5
Solubility	Soluble in deionized water, propylene glycol, SD alcohol 40, castor oil. Insoluble in cyclomethicone and isopropyl myristate.
Ricinoleamidopropyltrimonium methosulfate	
Molecular weight	508.756
Amido alkyl ether/glycol-ether	
Acetamidoethoxybutyl trimonium chloride	
Molecular weight	252.784
Acetamidoethyl PG-trimonium chloride	
Molecular weight	254.75
Appearance	Clear, pale straw-colored liquid
Odor	Sweet note
Boiling point (ºC)	105
Specific gravity	1.03
Solubility	Water
Alkanol	
Acetyl Carnitine HCl	
Molecular weight	239.093
Physical appearance	Crystalline powder
Carnitine	
Molecular weight	161.20
Physical appearance	White solid

Table 11. Physical and chemical properties

Property	Value
Melting point	210.00-212.00ºC
Solubility	Practically insoluble in acetone, ethyl acetate
Water	2500 g/l
Carnitine HCL	
Molecular weight	197.66
Physical appearance	Solid
Melting point (decomposes)	142ºC
Carnitine Hydroxycitrate	
Molecular weight	433.492
Carnitine PCA	
Molecular weight	290.313
Choline chloride	
Molecular weight	139.624
Appearance	White Crystals
Odor	Slight amine odor
Solubility	Water
pH	Neutral or slightly acidic (aq.)
Melting point	244-247ºC
Density	1.1 g/cm^3
Partition coefficient	-3.77 at 25°C
Lauroyl ethyltrimonium methosulfate	
Molecular weight	397.569
Myristoyl ethyltrimonium methosulfate	
Molecular weight	425.623
Palmitoyl Carnitine	
Molecular weight	399.608
Palmitoyl ethyltrimonium methosulfate	
Molecular weight	453.676
Stearoxypropyltrimonium chloride	
Molecular weight	106.134
Stearoyl ethyltrimonium methosulfate	
Molecular weight	481.730
Glycols	
Behenoyl PG-trimonium chloride	
Molecular weight	492.224
Appearance	Solid paste at 20ºC
Odor	Characteristic
pH	3-5 at 20ºC
Melting point (ºC)	50
Flash point (ºC)	>100
Density (g/cm^3)	0.95 @ 70ºC
Behenyl PG-trimonium chloride	
Molecular weight	479.248
Dihydroxypropyltrimonium chloride	
Molecular weight	169.65
Distearoylpropyl trimonium chloride	
Molecular weight	702.57
Isostearoyl PG-trimonium chloride	
Molecular weight	452.116
Lauroyl PG-trimonium chloride	
Molecular weight	351.956
Oleoyl PG-trimonium chloride	
Molecular weight	434.101
Palmitoyl PG-trimonium chloride	
Molecular weight	408.063
Stearyl PG-trimonium chloride	
Molecular weight	422.133
Stearoyl PG-trimonium chloride	
Molecular weight	436.117
Polymers containing trimonium	
Acrylamide/ethyltrimonium chloride acrylate/ethalkonium chloride acrylate copolymer	
Molecular weight of monomers	721.39
Acrylamidopropyl-trimonium chloride/acrylamide copolymer	
Molecular weight of monomers	259.388

Table 11. Physical and chemical properties

Property	Value
Acrylamidopropyl-trimonium chloride/acrylates copolymer	
Molecular weight of monomers	259.365
Acrylamidopropyl-trimonium chloride/acrylamide copolymer	
Molecular weight of monomers	259.39
Polyquaternium-14	
Molecular weight of monomers	301.401
Polyquaternium-28	
Molecular weight of monomers	302.257
Number-average molecular weight	>1000
Max low molecular weight species (%)	<1
Appearance (20°C; 101.3 kPa)	Hazy, highly viscous liquid
Glass-transition temperature	177°C
Specific gravity	1050 kg/m^3
Solubility	Freely soluble in water
Partition co-efficient (n-octanol/water; 20°C; log $P_{o/w}$))	<-1.2
Hydrolysis after 3 months as a function of pH	
pH 7, room temperature	7.2%
pH 7, 45°C	11.2%
pH 10, 45°C	17%
Adsorption/desorption (K_{OC})	1653
Polyquaternium-32	
Molecular weight of monomers	262.389
Polyquaternium-33	
Molecular weight of monomers	246.346
Physical appearance	Straw colored liquid
Odor	Mild amine odor
Flash Point	200ºF (93.3ºC)
Solubility	Water
Evaporation rate	<1 (butyl acetate = 1)
Polyquaternium-35	
Molecular weight of monomers	407.566
Polyquaternium-36	
Molecular weight of monomers	465.390
Polyquaternium-37	
Molecular weight of monomers	225.757
Polyquaternium-45	
Molecular weight of monomers	407.313
Polyquaternium-47	
Molecular weight of monomers	349.486
Polyquaternium-48	
Molecular weight of monomers	987.772
Polyquaternium-53	
Molecular weight of monomers	334.475
Polyquaternium-63	
Molecular weight of monomers	317.424
Polyquaternium-73	
Molecular weight of monomers	448.683
Polyquaternium-91	
Molecular weight of monomers	394.566

Table 12. Historical and current cosmetic product uses and concentrations for cetrimonium bromide, cetrimonium chloride and steartrimonium chloride.

Product Category	1994 uses (Andersen 1994)	2010 uses (FDA 2010)	2009 concentrations (Council 2009) (%)
Cetrimonium Bromide			
Eye makeup			
Eyeliners (834)	-	-	0.3
Eye shadow (1343)	1	7	0.1
Mascara (528)	-	1	-
Fragrance products			
Colognes and toilet waters (1426)	1	1	-
Powders (237)	3	-	-
Noncoloring hair care products			
Conditioners (1313)	13	27	0.1-3
Sprays/aerosol fixatives (321)	-	-	0.2
Rinses (34)	1	-	-
Shampoos (1487)	1	1	-
Tonics, dressings, etc. (1321)	3	7	0.1-0.2
Other (838)	-	-	0.3
Hair coloring products			
Bleaches (147)	-	-	2
Makeup			
Blushers (471)	1	5	-
Face powders (724)	3	4	-
Foundations (624)	1	-	-
Lipsticks (2045)	-	-	0.3
Personal hygiene products			
Underarm deodorants (623)	1	1	0.1
Other (925)	-	1	-
Shaving products			
Aftershave lotions (381)	-	-	0.1
Men's talcum (3)	1	-	-
Skin care products			
Skin cleansing creams, lotions, liquids, and pads (1528)	1	2	-
Face and neck creams, lotions, powder and sprays (1652)	1	-	-
Body and hand creams, lotions, powder and sprays (1875)	-	1	0.1
Moisturizers (2750)	3	3	-
Paste masks/mud packs (462)	-	1	-
Skin fresheners (267)	-	-	0.1
Suntan products			
Other (61)	1	-	-
Total uses/ranges for cetrimonium bromide	**37**	**68**	**0.1-2**
Cetrimonium chloride			
Baby products			
Other (149)	-	5	-
Bath products			
Soaps and detergents (1781)	-	3	0.09
Other (234)	-	1	-
Eye makeup			
Eye lotions (260)	-	-	0.0008
Eye makeup remover (133)	-	1	-
Fragrance products			
Colognes and toilet waters (1426)	-	-	0.1
Noncoloring hair care products			
Conditioners (1313)	86	435	0.1-10
Sprays/aerosol fixatives (321)	1	1	0.08-0.5
Straighteners (181)	-	17	0.2-0.5
Permanent waves (75)	2	6	0.2-0.4
Rinses (34)	3	12	0.08
Shampoos (1487)	1	43	0.004-0.5
Tonics, dressings, etc. (1321)	17	149	0.1-3

Table 12. Historical and current cosmetic product uses and concentrations for cetrimonium bromide, cetrimonium chloride and steartrimonium chloride.

Product Category	1994 uses (Andersen 1994)	2010 uses (FDA 2010)	2009 concentrations (Council 2009) (%)
Wave sets (60)	3	2	-
Other (838)	16	141	0.5-2
Hair coloring products			
Dyes and colors (2382)	18	92	0.2-0.3
Tints (6)	-	1	-
Rinses (40)	-	5	-
Shampoos (36)	2	3	-
Color sprays (7)	-	2	-
Bleaches (147)	-	7	-
Other (168)	-	7	0.3
Makeup			
Other (536)	-	-	0.3
Nail care products			
Other (137)	2	1	-
Personal hygiene products			
Underarm deodorants (623)	-	9	0.1
Shaving products			
Aftershave lotions (381)	-	1	-
Skin care products			
Skin cleansing creams, lotions, liquids, and pads (1528)	2	4	0.2
Depilatories (56)	-	-	0.1
Face and neck creams, lotions, powder and sprays (1652)	-	-	0.08-1
Body and hand creams, lotions, powder and sprays (1875)	2	1	0.2-3
Moisturizers (2750)	3	-	-
Skin fresheners (267)	2	1	-
Other (1446)	3	4	-
Suntan products			
Indoor tanning preparations (247)	-	3	-
Total uses/ranges for cetrimonium chloride	**162**	**959**	**0.0008-10**
Steartrimonium chloride			
Noncoloring hair care products			
Conditioners (1313)	3	19	2
Sprays/aerosol fixatives (321)	-	-	0.2
Permanent waves (75)	1	1	3
Rinses (34)	-	-	2-3
Shampoos (1487)	-	-	3
Tonics, dressings, etc. (1321)	-	4	0.3
Other (838)	2	7	-
Hair coloring products			
Dyes and colors (2382)	-	8	0.4-4
Tints (6)	-	-	0.06
Rinses (34)	-	1	-
Total uses/ranges for Steartrimonium chloride	**6**	**40**	**0.06-4**

Table 13. Frequency of use and concentration of the straight-chain alkyl trimonium ingredients

Product Category (Total number of products in each category (FDA 2009))	Frequency of use (FDA 2010)	Concentration of use (%) (Council 2010)
Behentrimonium chloride		
Baby products		
Shampoos (57)	-	0.4
Noncoloring hair care products		
Conditioners (1313)	349	2-5
Sprays/aerosol fixatives (321)	-	0.2-1
Straighteners (181)	1	0.8[a]
Permanent waves (75)	2	2
Rinses (34)	5	3
Shampoos (1487)	2	0.8-2
Tonics, dressings, etc. (1321)	41	0.2-3
Wave sets (60)	-	-
Other (838)	112	7
Hair coloring products		
Dyes and colors (2382)	252	2-3
Lighteners with color (22)	1	-
Other (168)	4	-
Personal hygiene products		
Douches (13)	1	-
Shaving products		
Shaving cream (128)	3	-
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1528)	-	0.9
Face and neck creams, lotions, powder and sprays (1652)	-	-
Moisturizers (2750)	6	-
Other (1446)	2	0.5
Total uses/ranges for behentrimonium chloride	**743**	**0.2-7**
Behentrimonium methosulfate		
Baby products		
Other (149)	2	0.3
Bath products		
Soaps and detergents (1781)	-	0.3
Noncoloring hair care products		
Conditioners (1313)	126	0.1-10
Sprays/aerosol fixatives (321)	-	0.8
Straighteners (181)	15	6[b]
Permanent waves (75)	3	-
Shampoos (1487)	3	0.002
Tonics, dressings, etc. (1321)	21	0.1-4
Other (838)	24	2
Hair coloring products		
Dyes and colors (2382)	16	3[c]
Tints (6)	1	-
Nail care products		
Cuticle softeners (30)	2	-
Personal hygiene products		
Underarm deodorants (623)	7	-
Other (925)	1	0.3
Shaving products		
Shaving cream (128)	1	
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1528)	-	0.2
Face and neck creams, lotions, powder and sprays (1652)	1	-
Body and hand creams, lotions, powder and sprays (1875)	18	0.3
Foot powders and sprays (46)	2	-
Moisturizers (2750)	27	-
Night creams, lotions, powder and sprays (386)	1	-

Table 13. Frequency of use and concentration of the straight-chain alkyl trimonium ingredients

Product Category (Total number of products in each category (FDA 2009))	Frequency of use (FDA 2010)	Concentration of use (%) (Council 2010)
Other (1446)	1	-
Total uses/ranges for behentrimonium methosulfate	**273**	**0.1-10**
Cetrimonium methosulfate		
Noncoloring hair care products		
Conditioners (1313)	41	0.2-2
Rinses (34)	2	-
Tonics, dressings, etc. (1321)	9	0.6-2
Other (838)	5	-
Hair coloring products		
Other (168)	5	-
Personal hygiene products		
Paste masks (mud packs) (462)	1	1
Total uses/ranges for Cetrimonium methosulfatee	**59**	**0.2-2**
Cocotrimonium chloride		
Noncoloring hair care products		
Conditioners (1313)	8	-
Shampoos (1487)	30	3
Tonics, dressings, etc. (1321)	33	-
Hair coloring products		
Shampoos (36)	8	-
Total uses/ranges for Cocotrimonium chloride	**49**	**3**
Cocotrimoium methosulfate		
Noncoloring hair care products		
Tonics, dressings, etc. (1321)	**8**	**-**
Other (838)	**2**	**-**
Total uses/ranges for cocotromonium methosulfate	**10**	**-**
Laurtrimonium chloride		
Eye makeup		
Eyebrow pencils (153)	-	0.001
Eyeliners (834)	2	0.001
Eye shadow (1343)	1	0.001
Mascara (528)	-	0.001
Noncoloring hair care products		
Conditioners (1313)	-	0.008-0.2
Sprays/aerosol fixatives (321)	-	0.003-0.01
Permanent waves (75)	-	0.09
Rinses (34)	1	-
Shampoos (1487)	2	-
Tonics, dressings, etc. (1321)	21	0.004
Hair coloring products		
Tints (6)	-	0.0005
Makeup		
Blushers (471)	1	0.001
Foundations (624)	1	0.003
Other (536)	-	0.001
Skin care products		
Body and hand creams, lotions, powder and sprays (1875)	2	
Total uses/ranges for laurtrimonium chloride	**35**	**0.0005-0.2**
Myrtrimonium bromide		
Eye makeup		
Eye makeup remover (133)	-	0.03
Shaving products		
Aftershave lotions (381)	-	0.1
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1528)	3	0.07
Face and neck creams, lotions, powder and sprays (1652)	-	0.03

Table 13. Frequency of use and concentration of the straight-chain alkyl trimonium ingredients

Product Category (Total number of products in each category (FDA 2009))	Frequency of use (FDA 2010)	Concentration of use (%) (Council 2010)
Skin fresheners (267)	2	-
Total uses/ranges for *myrtrimonium bromide*	**5**	**0.03-0.4**
Soytrimonium chloride		
Noncoloring hair care products		
Conditioners (1313)	3	-
Hair coloring products		
Dyes and colors (2382)	206	7
Shampoos (36)	7	-
Lighteners with color (22)	2	-
Other (168)	3	-
Total uses/ranges for soytrimonium chloride	**221**	**7**
Tallowtrimonium chloride		
Noncoloring hair care products		
Conditioners (1313)	28	0.03
Straighteners (181)	1	-
Permanent waves (75)	2	-
Shampoos (1487)	4	-
Tonics, dressings, etc. (1321)	11	0.1
Other (838)	2	
Hair coloring products		
Dyes and colors (2382)	41	-
Lighteners with color (22)		0.03
Total uses/ranges for tallowtrimonium chloride	**89**	**0.03-0.1**

[a] 0.4% after dilution.
[b] 3% after dilution.
[c] 1% after dilution.

Table 14. Frequency of use and concentration of the amide trimonium ingredients

Product Category (Total number of products in each category (FDA 2009))	Frequency of use (FDA 2009)	Concentration of use (%) (Council 2010)
Acetamidopropyl trimonium chloride		
Eye makeup		
Eye lotions (260)	1	-
Noncoloring hair care products		
Conditioners (1313)	1	-
Tonics, dressings, etc. (1321)	6	-
Other (838)	1	-
Total uses/ranges for *acetamidopropyl trimonium chloride*	9	**-**
Babassuamidopropyltrimonium methosulfate		
Noncoloring hair care products		
Conditioners (1313)	9	0.4
Sprays/aerosol fixatives (321)	-	0.08
Tonics, dressings, etc. (1321)	3	0.1
Total uses/ranges for babassuamidopropyltrimonium methosulfate	**12**	**0.08-0.4**
Behenamidopropyltrimonium methosulfate		
Noncoloring hair care products		
Conditioners (1313)	9	-
Sprays/aerosol fixatives (321)	-	0.5
Tonics, dressings, etc. (1321)	3	0.6
Total uses/ranges for behenamidopropyltrimonium methosulfate	**12**	**0.5-0.6**
Cinnamidopropyltrimonium chloride		
Noncoloring hair care products		
Conditioners (1313)	37	0.00001-2
Sprays/aerosol fixatives (321)	8	0.0008-3
Straighteners (181)	-	0.00008
Shampoos (1487)	28	0.007-2
Tonics, dressings, etc. (1321)	45	0.00001-2

Table 14. Frequency of use and concentration of the amide trimonium ingredients

Product Category (Total number of products in each category (FDA 2009))	Frequency of use (FDA 2009)	Concentration of use (%) (Council 2010)
Other (838)	17	-
Hair coloring products		
Dyes and colors (2382)	16	0.01
Shampoos (36)	1	-
Other (168)	1	-
Total uses/ranges for Cinnamidopropyltrimonium chloride	**153**	**0.00001-3**
Cocamidopropyltrimonium chloride		
Noncoloring hair care products		
Conditioners (1313)	-	3
Sprays/aerosol fixatives (321)	-	
Straighteners (181)	-	
Permanent waves (75)	-	
Rinses (34)	-	
Shampoos (1487)	-	0.004
Total uses/ranges for cocamidopropyltrimonium chloride	**-**	**0.004-3**
Lactamidopropyl trimonium chloride		
Noncoloring hair care products		
Conditioners (1313)	-	3
Tonics, dressings, etc. (1321)	1	-
Other (838)	2	
Total uses/ranges for lactamidopropyl trimonium chloride	**3**	**3**
Palmamidopropyl trimonium methosulfate		
Noncoloring hair care products		
Conditioners (1313)	7	2
Sprays/aerosol fixatives (321)	-	0.5
Shampoos (1487)	1	0.8
Tonics, dressings, etc. (1321)	2	2
Total uses/ranges for palmamidopropyl trimonium methosulfate	**10**	**0.5-2**
Palmitamidopropyltrimonium chloride		
Noncoloring hair care products		
Conditioners (1313)	2	0.9-2
Other (838)	3	-
Skin care products		
Moisturizers (2750)	1	-
Total uses/ranges for palmitamidopropyltrimonium chloride	**6**	**0.9-2**
Undecylenamidopropyltrimonium methosulfate		
Noncoloring hair care products		
Shampoos (1487)	1	1
Skin care products		
Foot powders and sprays (46)	1	-
Total uses/ranges for undecylenamidopropyltrimonium methosulfate	**2**	**1**

Table 15. Frequency of use and concentration of the alkanol trimonium ingredients and related ethers/esters/acids

Product Category (Total number of products in each category (FDA 2009))	Frequency of use (FDA 2009)	Concentration of use (%) (data not available)
Acetyl carnitine HCl		
Eye makeup		
Lotion (260)	5	-
Make up		
Lipstick (2045)	1	-
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1528)	2	-
Face and neck creams, lotions, powders and sprays (1652)	1	-
Body and hand creams, lotions, powder and sprays (1875)	2	-
Moisturizers (2750)	16	-
Night creams, lotions, powder and sprays (386)	1	-
Other (1446)	1	-
Total uses/ranges for acetyl carnitine HCl	**30**	**-**
Carnitine		
Eye makeup		
Lotion (260)	2	-
Noncoloring hair care products		
Wave sets (60)	1	
Other (838)	1	-
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1528)	1	-
Body and hand creams, lotions, powder, and sprays (1875)	18	-
Moisturizers (2750)	1	-
Night creams, lotions, powder and sprays (836)	2	-
Other (1446)	4	-
Total uses/ranges for carnitine	**30**	**-**
Carnitine HCl		
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1528)	1	-
Total uses/ranges for carnitine HCl	**1**	**-**
Palmitoyl carnitine		
Skin care products		
Face and neck creams, lotions, powders and sprays (1652)	1	-
Body and hand creams, lotions, powder and sprays (1875)	3	-
Moisturizers (2750)	1	-
Total uses/ranges for palmitoyl carnitine	**5**	**-**
Carnitine hydroxycitrate		
Skin care products		
Body and hand creams, lotions, powder and sprays (1875)	2	-
Other (1446)	2	-
Total uses/ranges for carnitine hydroxycitrate	**4**	**-**

Table 16. Frequency of use and concentration of the glycol trimonium ingredients.

Product Category (Total number of products in each category (FDA 2009))	Frequency of use (FDA 2009)	Concentration of use (%) (data not available)
Behenoyl PG-trimonium chloride		
Noncoloring hair care products		
Conditioners (1313)	3	-
Rinses (34)	1	-
Other (838)	1	-
Total uses/ranges for behenoyl PG-trimonium chloride	**5**	**-**
Dihydroxypropyltrimonium chloride		
Skin care products		
Body and hand creams, lotions, powder and sprays (1875)	3	0.05
Total uses/ranges for dihydroypropyltrimonium chloride	3	**0.05**
Lauroyl PG-trimonium chloride		
Noncoloring hair care products		
Conditioners (1313)	1	-
Total uses/ranges for lauroyl PG-trimonium chloride	**1**	**-**

Table 17. Frequency of use and concentration of the trimonium polymers.

Product Category (Total number of products in each category (FDA 2009))	Frequency of use (FDA 2009)	Concentration of use (%) (complete data not available)
Acrylamidopropyltrimonium chloride/acrylamide copolymer		
Noncoloring hair care products		
Rinses (34)	1	-
Shampoos (1487)	2	0.04
Tonics, dressings, etc. (1321)	3	-
Other (838)	1	
Total uses/ranges for acrylamidopropyltrimonium chloride/acrylamide copolymer	7	**0.04**
Polyquaternium-28		
Noncoloring hair care products		
Conditioners (1313)	1	-
Permanent waves (75)	1	-
Shampoos (1487)	7	-
Tonics, dressings, etc. (1321)	7	-
Other (838)	5	-
Hair coloring products		
Dyes and colors (2382)	44	-
Skin care products		
Other (1446)	8	-
Total uses/ranges for polyquaternium-28	73	-
Polyquaternium-32		
Noncoloring hair care products		
Conditioners (1313)	23	-
Tonics, dressings, etc. (1321)	6	-
Other (838)	1	-
Personal hygiene products		
Other (925)	1	-
Skin care products		
Moisturizers (2750)	1	-
Total uses/ranges for polyquaternium-32	32	-
Polyquaternium-35		
Noncoloring hair care products		
Permanent waves (75)	1	-
Total uses/ranges for polyquaternium-35	1	
Polyquaternium-37		
Noncoloring hair care products		
Conditioners (1313)	70	-
Straighteners (181)	1	-
Rinses (34)	2	-
Tonics, dressings, etc. (1321))	45	-
Other (838)	35	-
Hair coloring products		
Dyes and colors (2382)	1	-
Bleaches (147)	2	-
Other (168)	16	-
Make up		
Other (536)	1	-
Nail care products		
Nail creams and lotions (15)	1	-
Other (137)	3	-
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1528)	4	-
Face and neck crams, lotions, powder and sprays (1652)	2	-
Body and hand crams, lotions, powder and sprays (1875)	1	-
Moisturizers (2750)	23	-
Other (1446)	3	-
Suntan Products		
Indoor tanning preparations (247)	2	-
Total uses/ranges for polyquaternium-37	**213**	-
Polyquaternium-47		
Baby products		

Table 17. Frequency of use and concentration of the trimonium polymers.

Product Category (Total number of products in each category (FDA 2009))	Frequency of use (FDA 2009)	Concentration of use (%) (complete data not available)
Baby shampoos (57)	1	-
Noncoloring hair care products		
Conditioners (1313)	3	-
Shampoos (1487)	4	-
Tonics, dressings, etc. (1321)	3	-
Hair coloring products		
Dyes and colors (2382)	5	-
Hair lighteners with colors (22)	1	-
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1528)	3	-
Total uses/ranges for polyquaternium-47	**20**	**-**

*Waiting for data from the Council.

Table 18. Acute oral toxicity studies of cetrimonium chloride and steartrimonium chloride.[55]

Species	N	LD_{50}	Notes
Cetrimonium chloride			
Wistar rat	10 (5/sex)	Male rats – 2970 mg/kg Female rats – 1550 mg/kg Male and female rats – 2410 mg/kg	As Genamin CTAC (29% cetrimonium chloride). Moderately toxic.
Sprague-Dawley rat	10 (5/sex)	~2000 mg/kg	As Quartanim 60W25 (25% cetrimonium chloride).
Steartrimonium chloride			
Wistar rats	10 (5/sex)	~700 mg/kg	Genamin STAC (79.2% steartrimonium chloride in isopropanol). Most deaths occurred on the first day.
Mixture – cetrimonium choride/steartrimonium choride			
Sprague Dawley rat	10 (5/sex)	>2000 mg/kg	As Quartanim 86W (28% steartrimonium chloride:cetrimonium chloride [80:20]).

Table 19. Intravenous LD_{50} of surface-active alkyltrimethylammonium bromides.[72]

	Mouse		Rat	
Surfactant	μmol/kg	mg/kg	μmol/kg	mg/kg
Decyltrimethylammonium bromide (C_{10})	10 (9-11)	2.8	19 (18-20)	5.5
Dodecyltrimethylammonium bromide (C_{12})	17 (15-19)	5.2	22 (18-26)	6.8
Tetradeccyltrimethylammonium bromide (C_{14})	40 (36-44)	12.0	45 (42-48)	44.0
Cetyltrimethlammonium bromide (C_{16})	87 (81-93)	32.0	120 (112-128)	44.0
Eicosyltrimethylamonium bromide (C_{20})	48 (45-50)	20.0	-	-

Table 20. Ocular irritation test of cetrimonium chloride using New Zealand rabbits.

Species/test (n)	Test substance	Results	Reference
Male New Zealand albino rabbits (n = 3)	Cetrimonium chloride (10% in 0.5% methylcellulose in purified water; 0.1 ml). Rinsed after 30 sec.	Grade 2 corneal opacity observed in 1 rabbit at 24 and 48 h and grade 1 on day 22. 1 rabbit had grade 1 irititis from 1 h to day 7. Grade 1-3 swelling between 1 and 72 h; persisted until days 5, 9 and 22. Conclusion: cetrimonium chloride (10%) caused irreversible ocular damage.	SCCP[55]
Male New Zealand albino rabbits (n = 3)	Cetrimonium chloride (80%) in 0.5% methylcellulose in purified water (0.1 ml). Final concentration 6.25%. Rinsed after 30 sec.	Corneal opacity at 24 h. Irititis at 24 h, 1 rabbit until 72 h. Conjuctival irritation (redness) from 1 – 72 h; subsided after 7, 7, and 15 days. Swelling between 1 and 72 h; subsided after 5, 6, and 18 days. Conclusion: cetrimonium chloride (6.25%) caused conjunctival irritation.	SCCP[55]
Male New Zealand albino rabbits (n = 3)	Cetrimonium chloride (3%) in 0.5% methylcellulose in purified water (0.1 ml). Rinsed after 30 sec.	No corneal opacity. Irititis observed at 24 h in all rabbits and 1 at 72 h. conjunctival irritation (redness) at 1 h (3/3), 24 h (2/3), and 48 h (1/3). Conclusion: cetrimonium chloride (3%) caused transient conjunctival irritation.	SCCP[55]
Rabbits (n = 3)	Cetrimonium chloride (10%)	MAS score of 69.0. Day 1 49.7. Damage was irreversible.	Gautheron et al. 1994[81]

Table 21. Genotoxicity tests of choline chloride.[22]

Test		Concentration	Results
Ames test (2 separate tests)	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 and *E. coli* WP2uvrA	Up to 10,000 µg/plate and 5000 µg/plate with and without metabolic activation	No toxicity, no gene mutations
Chromosomal aberration test	Chinese hamster ovary cells	50 and 500 µg/ml with and without S9	Increase in simple aberrations in the absence of S9
Chromosomal aberration test (2 separate tests)	Chinese hamster ovary cells	Up to 5000 µg/ml.	Cytotoxicity began at 5000 µg/ml
Sister chromatid exchange	Chinese hamster ovary cells	500 µg/ml	No toxicity, no gene mutations
Sister chromatid exchange	Chinese hamster ovary cells	5000 µg/ml	Cytotoxicity began at 5000 µg/ml with S9, increased in SCEs with S9 was sporadic and not dose related
Sister chromatid exchange	Chinese hamster ovary cells	Up to 5000 µg/ml	No increase in SCEs
Gene conversion assay	*Saccharomyces cerevisiae* (D4)	12.5 – 50 mg/ml with and without metabolic activation	Negative

Table 22. Human dermal irritation studies of cetrimonium chloride.

Test (concentration or amount)	Results	Reference
Webril (0.2 ml)	Non-irritating	[115]
Hill Top (0.2 ml)	Non-irritating	[115]
Finn (0.4 ml)	Non-irritating	[115]
Van der Bend (0.03 ml)	Non-irritating	[115]
4-h Patch test (3.5%, 7.5%, 8.8%)	Moderate irritant	[116]
24-h Patch test (3.25%)	Slightly to moderately irritating	[55]
1-h Patch test (2.5%)	Minimal skin irritant	[55]
24-h Patch test (cosmetic formulation 3.52%; 50% solution)	Non-irritating	[55]
48-h Patch test (cosmetic formulation 3.2%; 50% solution)	Non-irritating	[55]
24-h Patch test (1%)	Non-irritating	[55]
24-h Patch test (formulation 2.0; 50% solution)	Non-irritating	[55]
24-h Patch test (cosmetic formulation 3.01%; 25% aqueous solution)	Minimally irritating	[55]
24-h Patch test (cosmetic formulation 4%; 10% aqueous solution)	Not irritating	[55]
24-h Patch test (styling gel formulation 0.5%; 25%, 50%, 75%, 100% solution)	Non-irritating	[55]