Safety Assessment of Titanium Complexes as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: March 15, 2019
Panel Date: April 8-9, 2019

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

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: March 15, 2019
Subject: Draft Final Report on Titanium Complexes

The draft final report on titanium complexes (*organo042019FR)* is attached for the Panel's consideration. At the September 24-25, 2018 CIR Expert Panel (Panel) Meeting, the Panel issued a tentative report with a split conclusion for public comment: Isopropyl Titanium Triisostearate is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when used as a surface modifier. The data are insufficient to determine the safety of the following 4 ingredients: Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, and Titanium Salicylate.

The Panel determined that the following data are needed to assess the safety of these 4 ingredients:

- Maximum use concentrations
- Methods of manufacture
- Impurities
- 28-day dermal toxicity data
    - Depending on the results of these studies, various systemic toxicity data may also be needed
- Genotoxicity data
- Skin irritation and sensitization data at maximum cosmetic use concentrations, except for Titanium Citrate

Furthermore, the Panel noted that if data indicate the presence of significant levels of residual Isopropyl Titanium Triisostearate result with use as a surface modifier, 28-day dermal toxicity data and genotoxicity data would then be needed to evaluate the safety of this ingredient. The same would apply to any other identified use(s) of this ingredient that would yield free Isopropyl Titanium Triisostearate in the product formulation.

The Panel requested clarification of the following:
(1) Isopropyl Titanium Triisostearate is only being used as a surface modifier,
(2) the other titanium complex ingredients are not being used as surface modifiers, and
(3) surface modification does not result in any appreciable residual Isopropyl Titanium Triisostearate in the final product.

The identification of whether or not Isopropyl Titanium Triisostearate was used as a surface modifier in product formulations tested, text added to the report discussion, and the following unpublished data, received in response to the Panel's data requests, are highlighted in the report text:

- Use concentration data on Isopropyl Titanium Triisostearate (with confirmation that all relate to use as a surface modifier) (*organo042019data1)*
- HRIPT on a foundation containing 0.433% Isopropyl Titanium Triisostearate (used as a surface modifier) (*organo042019data2)*
- HRIPT on a foundation containing 0.348% Isopropyl Titanium Triisostearate (used as a surface modifier) (*organo042019data2)*
- Summaries of HRIPTs on products containing Isopropyl Titanium Triisostearate (0.276%, 0.281%, and 0.337%) (used as a surface modifier) (*organo042019data3)*

- Memorandum from the Council stating whether or not Isopropyl Titanium Triisostearate was used as a surface modifier in HRIPT data previously submitted (*organo042019data4)*

However, data relating to the presence of residual, unreacted Isopropyl Titanium Triisostearate in products in which this ingredient is being used as a surface modifier were not provided. Until these data are provided, whether or not the use concentration data represent the bound ingredient or the bound + unreacted ingredient remains unknown. Information on whether or not the remaining ingredients in this safety assessment function as surface modifiers also has not been provided, and the same is true for the safety test and other data on these ingredients that were requested by the Panel.

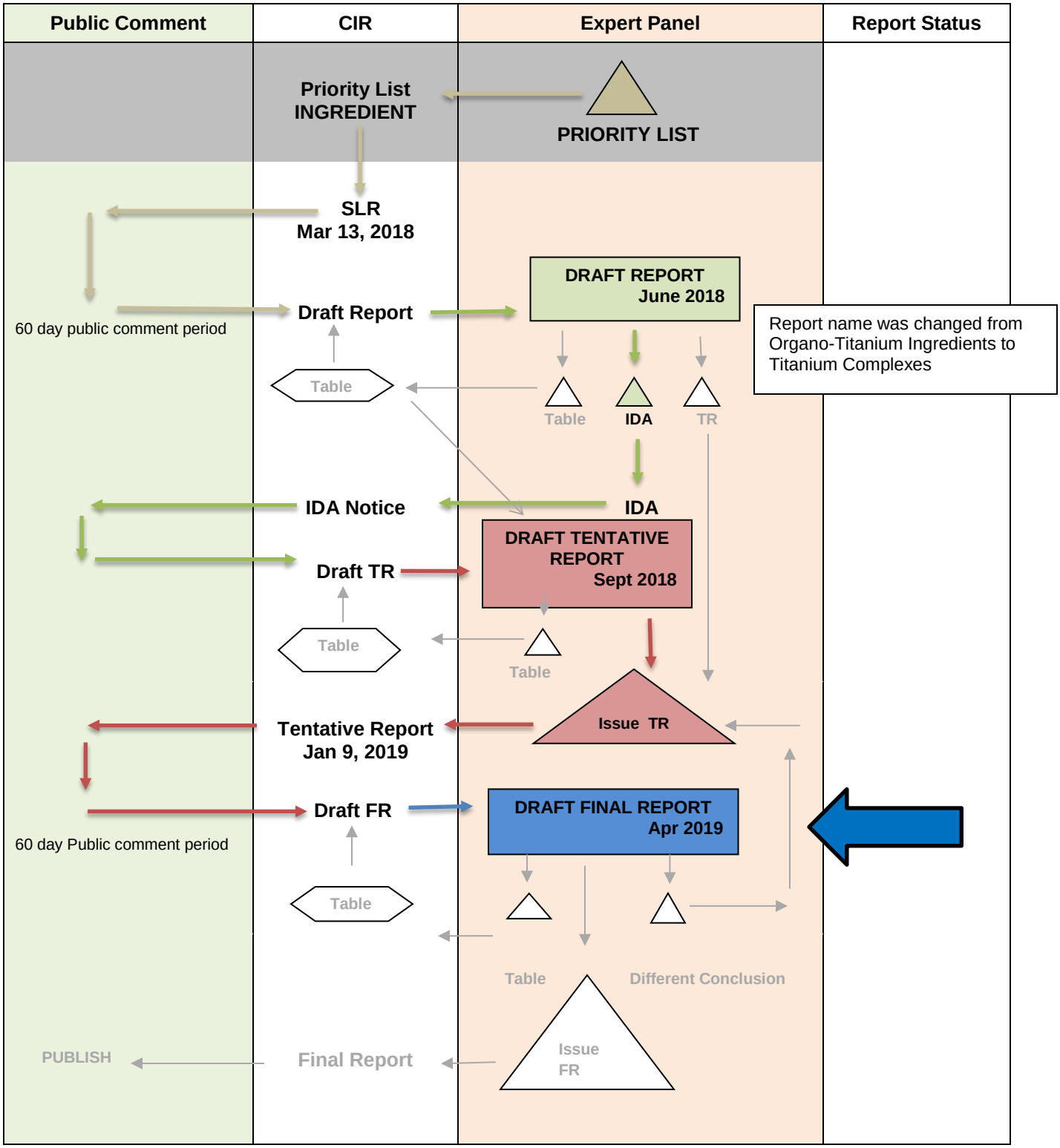
Also included in this package for your review are the CIR report history (*organo042019hist*), flow chart (*organo042019flow*), literature search strategy (*organo042019strat*), ingredient data profile (*organo042019prof*), 2019 FDA VCRP data (*organo092019FDA*), minutes from the June 2018 and September 2018 Panel Meetings (*organo042019min*), and comments that were received from the Personal Care Products Council (Council) prior to the September 2018 Panel meeting and after issuance of the tentative report (*organo042019pcpc1* and *organo042019pcpc2*, respectively*)*. All comments received from the Council have been addressed.

In the absence of data on unreacted, residual Isopropyl Titanium Triisostearate in cosmetic products in which this ingredient functions as a surface modifier, the Panel should determine whether or not a final report with the conclusion stated above should be issued, or whether a qualification on the safe as used conclusion for Isopropyl Titanium Triisostearate needs to be added.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Titanium Complexes

MEETING April 2019



CIR History of:

Organo-Titanium Ingredients (name changed to Titanium Complexes)

A Scientific Literature Review (SLR) on Organo-Titanium Ingredients was issued on March 13, 2018.

Draft Report, Teams/Panel: June 4-5, 2018

The draft report also contains the following data that were received from the Council before/after announcement of the SLR: use concentration data on Organo-Titanium Ingredients; a human skin irritation test on a concealer containing 0.4% Isopropyl Titanium Triisostearate; a human maximization test on a foundation containing 0.4% Isopropyl Titanium Triisostearate; an *in vitro* ocular irritation assay on foundation topcoats containing 0.102% Isopropyl Titanium Triisostearate; a human phototoxicity test on a pressed powder containing 0.004% Isopropyl Titanium Triisostearate; and an HRIPT on a foundation topcoat containing 0.102% Isopropyl Titanium Triisostearate. These data are included in the Draft Report, and comments that were received from the Council have been addressed.

After discussing the data included in the Draft Report, the Panel issued an Insufficient Data Announcement (IDA) with the following data requests:

Isopropyl Titanium Triisostearate

- 28-day dermal toxicity data
  - Depending on the results of this study, additional systemic toxicity data may be needed
- Mammalian genotoxicity data

Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, and Titanium Salicylate

- Use concentration data
- Method of manufacture and impurities
- 28-day dermal toxicity data; depending on the results of this study, additional systemic toxicity data may be needed
- Skin irritation and sensitization data at cosmetic use concentrations

Draft Tentative Report, Teams/Panel: September 24-25, 2018

The following data on black iron oxide with 2% Isopropyl Titanium Triisostearate were received in response to the IDA: (1) Acute oral toxicity (rats), (2) Skin irritation (rabbits), and (3) Ocular irritation (rabbits). These data have been added to the safety assessment. Comments that were received from the Council prior to the June Panel meeting have been addressed.

The Panel issued a tentative report for public comment with a split conclusion:

Isopropyl Titanium Triisostearate is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when used as a surface modifier. The data are insufficient to determine the safety of the following 4 ingredients: Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, and Titanium Salicylate.

The Panel determined that the following data are needed to assess the safety of these 4 ingredients:

- Maximum use concentrations
- Methods of manufacture
- Impurities
- 28-day dermal toxicity data
  - Depending on the results of these studies, various systemic toxicity data may also be needed
- Genotoxicity data
- Skin irritation and sensitization data at maximum cosmetic use concentrations, except for Titanium Citrate

Skin irritation and sensitization data on Titanium Citrate previously requested are no longer needed because the Panel determined that results of a study on 37 patients (all suspected of having titanium allergy) patch tested with 0.16% and 0.32% Titanium Citrate were sufficient for evaluating these endpoints.

Submitted method of manufacture data demonstrate that as a surface modifier in cosmetic products, Isopropyl Titanium Triisostearate is covalently bound to a pigment (e.g., black iron oxide). Thus, the presence of any residual or unreacted Isopropyl Titanium Triisostearate in the product formulation would be considered an impurity.

The Panel noted that if data indicating the presence of significant levels of residual Isopropyl Titanium Triisostearate resulting from use as a surface modifier are provided, 28-day dermal toxicity data and genotoxicity data would then be needed to evaluate the safety of this ingredient. The same would apply to any other identified use(s) of this ingredient that would yield free Isopropyl Titanium Triisostearate in the product formulation. The Panel requested clarification of the following: (1) Isopropyl Titanium Triisostearate is only being used as a surface modifier, (2) the other titanium complex ingredients are not being used as surface modifiers, and (3) surface modification does not result in any appreciable residual Isopropyl Titanium Triisostearate in the final product.

The Panel requested that in addition to addressing their concerns relating to surface modifier chemistry, that industry determine the form of Isopropyl Titanium Triisostearate (bound to pigment or not) that is associated with the use concentration data that were provided and determine the form (and resultant concentrations) of Isopropyl Titanium Triisostearate in the unpublished product formulation safety test data that were provided.

Draft Final Report, Teams/Panel: April 8-9, 2019

Comments that were received from the Council have been addressed, and the following unpublished data (received from the Council) have been added to the safety assessment:

- Use concentration data on Isopropyl Titanium Triisostearate
- HRIPT on a foundation containing 0.433% Isopropyl Titanium Triisostearate (used as a surface modifier)
- HRIPT on a foundation containing 0.348% Isopropyl Titanium Triisostearate (used as a surface modifier)
- Summaries of HRIPTs on products containing Isopropyl Titanium Triisostearate (0.276%, 0.281%, and 0.337%) (used as a surface modifier)

In response to the Panel's data requests, confirmation of whether or not Isopropyl Titanium Triisostearate was used as a surface modifier in the product formulation test data provided by the Council was received. With the exceptions of HRIPT data on an experimental product (never marketed) containing 1.4% Isopropyl Titanium Triisostearate, phototoxicity data (humans) on a pressed powder containing 0.0004% Isopropyl Titanium Triisostearate, and acute oral and dermal toxicity, genotoxicity, and skin and ocular irritation data on an Isopropyl Titanium Triisostearate trade name material (98% Isopropyl Titanium Triisostearate and < 2% isopropyl alcohol), the ingredient Isopropyl Titanium Triisostearate was used as a surface modifier in all of the studies that were provided by the Council. Confirmation that the Council's use concentration data on Isopropyl Titanium Triisostearate relate to the use this ingredient as a surface modifier was also received. However, data relating to the presence of residual, unreacted Isopropyl Titanium Triisostearate in products in which this ingredient is being used as a surface modifier were not provided. Until these data are provided, whether or not the use concentration data represent the bound ingredient or the bound + unreacted ingredient remains unknown. Information on whether or not the remaining ingredients in this safety assessment function as surface modifiers also has not been provided, and the same is true for the safety test and other data on these ingredients that were requested by the Panel.

Data Profile on Titanium Complexes for April 8th-9th 2019 Panel – Wilbur Johnson

	Dermal Penetration			Nail Penetration	Penetration Enhancement	ADME					Acute Toxicity			Short-Term Toxicity	Sub-Chronic Toxicity	Chronic Toxicity	DART		Genotoxicity	Carcinogenicity	Other Relevant Studies		Dermal Irritation*	Dermal Sensitization /Photosensitization		Ocular Irritation *		Clinical Studies	Case Reports		Epidemiology Studies
	In Vivo -Animal	In Vitro-Human	In Vivo-Human	In Vitro-Human	In Vitro-Animal	In Vitro	Animal-Dermal	Animal-Oral	Animal-Inhalation	Human-Oral	Animal-Dermal	Animal-Oral	Animal-Injection	Animal	Animal	Animal	In Vitro	In Vivo	In Vitro/In Vivo	In Vivo	In Vitro	In Vivo-Animal	Animal/Human/In vitro	Animal	Human	In Vitro	Animal	Human-MulticenterStudy	Human-Dermal	Human-Inhalation	Human
Isopropyl Titanium Triisostearate											X	**X**							**X**				**X**		**X**	**X**	**X**				
Titanium Citrate						**X**															**X**										
Titanium Ethoxide												**X**																			
Titanium Isostearates																															
Titanium Salicylate										**X**			**X**	**X**									**X**								

X = data

[Titanium Complexes – 1/8/2018; 8/6-7/2018; 3/5/2019]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECET-OC	Web
Isopropyl Titanium Triisostearate	61417-49-0	Yes	1516/8	1/0	2/0	No	No	No	No	No	Yes	No	No	No	No	No	No	
Titanium Citrate		Yes	467/5	38/2	14/0	Yes	No	No	No	No	No	No	No	No	No	No	No	
Titanium Ethoxide	3087-36-3	Yes	1030/3	7/0	2/1	No	No	Yes	No	No	No	No	No	No	No	No	No	
Titanium Isostearates		Yes	99/0	1/0	1/0	No	No	No	No	No	No	No	No	No	No	No	No	
Titanium Salicylate		Yes	26/5	18/0	2/1	Yes	No	No	No	No	No	No	No	No	No	No	No	

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

[*identify total # of hits /# hits that were useful or examined for usefulness*]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/

RIFM (the Research Institute for Fragrance Materials) should be contacted

Qualifiers
Absorption
Acute
Allergy
Allergic
Allergenic
Cancer
Carcinogen
Chronic
Development
Developmental
Excretion
Genotoxic
Irritation
Metabolism
Mutagen
Mutagenic
Penetration
Percutaneous
Pharmacokinetic
Repeated dose
Reproduction
Reproductive
Sensitization
Skin
Subchronic
Teratogen
Teratogenic
Toxic
Toxicity
Toxicokinetic
Toxicology
Tumor

Day 1 of the June 4-5, 2018 CIR Expert Panel Meeting – Dr. Belsito's Team

Titanium Complexes

DR. BELSITO: Okay, great. Let's move on to the organo-titanium ingredients. This is the first time we're seeing these. And in addition to what was in our report, we did get some Wave 2 data on isopropyl titanium triisostearate, which seems to be the only one that is in cosmetic use.

And my first question to Dan is, is this a proper group? Because looking at these, they look all extremely different to me, other than the fact that there is titanium someplace in them. And the only data we have is on the isopropyl titanium triisostearate, and can we read across with that?

DR. LIEBLER: It's the only one used.

DR. BELSITO: It's the only one used, too, but it's the only data. So, can we read across from that? Because molecularly these things look totally different to me.

DR. LIEBLER: Hang on, I'm looking to see if I didn't have a note.

DR. KLAASSEN: That's the way I saw it too.

DR. LIEBLER: Don, I did consider your issue, because I knew you would ask me about did these things all belong. And I felt that the driver here was the titanium. And therefore, the diversity in the organic piece was acceptable to me. And if things were not going to be supported, they would be insufficient, rather than thrown out of the report. My logic was to save the titanium.

DR. BELSITO: I'd like to save the titanic.

DR. LIEBLER: We will save the titanium.

DR. BELSITO: Okay. And then the next question is, is there a reason why titanium salicylate is here and not in our salicylate report?

DR. LIEBLER: The titanium probably. I mean, I would argue that it would be in this report, not the salicylate report.

DR. BELSITO: You believe it more appropriately belongs in this one?

DR. LIEBLER: Oh, I think so.

DR. KLAASSEN: I agree.

DR. BELSITO: Okay, just asking these questions. I'm a naive little chemist, learning from the pros. We did get chemical and physical properties on the triisostearate in Wave 2. It's not likely to be absorbed, so do we need systemic tox endpoints? We have a negative Ames but no mammalian. I mean, we really have very limited data here. But we don't have impurities on the isostearate.

MR. JOHNSON: Dr. Belsito, we did receive impurities data on a titanium compound that's used in the manufacture of isopropyl titanium triisostearate.

DR. BELSITO: Did I miss that in Wave 2.

DR. SNYDER: Wave 2. Yeah.

DR. BELSITO: Oh yeah, okay.

DR. LIEBLER: These are impurities in an intermediate, in the manufacture of the triisostearate, the isopropoxide. And it's better than nothing. It's not ideal.

DR. BELSITO: I guess the question is, given what we have on physical properties and impurities, would we expect dermal absorption because we basically have no toxicity data? And this is just for the triisostearate, because we essentially have no data on any of the others. And we have a negative Ames for the triisostearate, but we do not have a mammalian.

We have an HRIPT that clears the skin use for the triisostearate, so my due diligence is done. It's safe for sensitization. But I need your input for other tox endpoints, the fact that we have no data on them.

DR. LIEBLER: The triisostearate's a little under 1000 molecular weight. It's a triisostearate. It's arguably within the range where absorption would be low, but I can't say it's not going to be absorbed.

DR. BELSITO: Twenty-eight day dermal needed?

DR. LIEBLER: Yeah.

DR. SNYDER: Yeah. This is the first time we've seen it, so we can just go with our normal.

DR. BELSITO: Okay. So, triisostearate we needed 28-day dermal. And if absorbed, other toxicity endpoints. Do we need a mammalian genotox? All we have is Ames.

DR. LIEBLER: Yes.

DR. BELSITO: Okay. So, the triisostearate is insufficient for 28-day dermal. And depending upon if there's absorption, other toxicity endpoints may be needed, and a genotox and mammalian system.

We have no data on any of the others. Are we able to read across from the triisostearate to those; or are those data insufficient?

DR. LIEBLER: The only one I would be comfortable reading across would be the titanium isostearates. In general, I don't like reading across when there are inorganic's involved. I think that these compounds will be probably pretty similar, in terms of the titanium part of their toxicology. And it's going to be ADME differences between these. I mean, the citrate ethoxide is just ethanol, basically, a salicylate. Those aren't going to be significant drivers of any health effects of these.

I think we should ask for the relevant data on all of these. And if we don't get them, they're going to be insufficient. I don't think we can do a lot of read across.

DR. EISENMANN: My question is, if titanium is what is holding this group together, do you want to see data on titanium? Should he look for genotoxicity on titanium? Because if you pull off the isostearate groups, the organic part --

DR. LIEBLER: I'm not sure how relevant those would be. These are all going to be titanium +4 molecules. Your chemistry description, I think, is a little too vague and suggest that there are a lot of different oxidations states with these materials. And I don't think that's true. I mean, it's true that titanium has multiple oxidation states, but from looking into these, these all appear to be Ti+4.

To get back to Carol's question, are there other Ti+4 relevant compounds for which genotox data could be useful read across. I'm not sure, but they would be salts. And these aren't really like salts, these are almost more sort of coordinate -- they use the term almost covalent. But they're coordinate bonded molecules that might have very different effects on how the titanium behaves.

I wouldn't want to try and bring in titanium salt data and try and use that to read across for genotox. In general, I don't like read across with inorganics, it's just too unpredictable.

DR. BERGFELD: Can I ask a question. Titanium is now used as a sunblock, and there's lot of information in the OTC/FDA group regarding titanium.

DR. BELSITO: But we determined titanium dioxide is very different from this titanium.

DR. BERGFELD: I know but -- that's what I'm asking because there is a titanium salicylate.

DR. BELSITO: I know, but --

DR. BERGFELD: And the photosensitivity studies demonstrate that it does absorb.

DR. BELSITO: But I thought it was noted that the valency of this titanium was quite different from titanium dioxide, which is why we weren't including this in the report, is that correct?

DR. LIEBLER: Titanium dioxide is also +4, but it's just titanium bound into oxygen as opposed to these alkoxy substituents; and those are really chemically pretty different. So, titanium dioxide's really pretty inert. And that's one of the values of it.

DR. BERGFELD: Is the titanium salicylate though -- is that different? I'm not a chemist.

DR. LIEBLER: Yeah.

DR. BERGFELD: Than titanium dioxide?

DR. LIEBLER: Right. Right. Titanium dioxide, think of it as titanium with two tightly bonded oxygen, double-bonded oxygen. That's sort of what titanium dioxide kind of looks like.

These are these four coordinate complexes of titanium. They can exchange ligands more readily. Whereas, the titanium dioxide is titanium dioxide; it's pretty insoluble, which is one of the other reason why it works for a sunscreen, et cetera.

But these are really different molecules. I would not want to bring titanium dioxide data in to try and read across to anything in this report. I don't think it would help us.

DR. BERGFELD: Right. I'd just like to make another statement. The FDA dealt with the sunscreen absorbers and blockers basically for years, the titanium and zinc. And they did not clarify them as FDA approved for the OTC, I think until more recently. And the reason being was, the companies producing these products made nanoparticles.

And so instead of having something that was sitting on the surface of the skin it now penetrated and it was toxic. So, in these smaller particles, there is absorption and there is at least localized toxicity if not systemic. And there is data on that.

DR. SADRIEH: No, nanoscale titanium dioxide does not penetrate the skin. We've done studies on that.

DR. BERGFELD: Is that where it stands right now?

DR. SADRIEH: Yes. Yes.

DR. LIEBLER: It doesn't penetrate the stratum corneum?

DR. SADRIEH: It does not.

DR. LIEBLER: Okay.

DR. SADRIEH: No.

DR. BERGFELD: I went to one of their big conferences and they just demonstrated it on -- like microscopy and other studies said it did locally.

DR. SADRIEH: Well, I don't know, I mean we did a study on pigs and it didn't go through the skin. I don't know what new studies they -- titanium dioxide, that's what I wanted to say.

I just had a question. The question was raised initially about grouping them together; and you said it was okay to group them together, but you don't like to do read across from them.

DR. LIEBLER: No, no, no. I didn't mean -- when I was asked about grouping them together, I was really asking about including them in the report.

And yes, I think we can include them in the report, because they're in the dictionary. They're all organo-titanium compounds. That doesn't mean necessarily that I'm withdrawing the judgement that they are chemically similar enough to read across the data between them. Does that make sense? No?

DR. SADRIEH: I guess I don't know. You're saying that some data for some and -- normally you don't have data on all the things that you group anyway. So, you take data from some and then you apply it to all of them. I mean, in my opinion, your reports are such that when you group them together, you are doing read across.

DR. LIEBLER: No. No, that's not true. It's a different consideration. Having them in the report means that they have some unifying feature that justifies their grouping. And the unifying feature might be a chemical part of a molecule, in this case the titanium part. It also might be use, some combination of those.

But that doesn't necessarily mean that we can read across all of the ingredients in the report, or even most of the ingredients in the report. It doesn't necessarily apply. That's yet another bar beyond grouping them together in the report.

DR. BELSITO: Okay. So, let me go back. What I'm hearing Dan, is that you feel, in terms of these five ingredients, that we can read across all of the information we have on isopropyl titanium triisostearate which is really the only one we have information on --

DR. LIEBLER: Right.

DR. BELSITO: -- to titanium isostearate.

DR. LIEBLER: Correct.

DR. BELSITO: However, the citrate, the ethoxide and the salicylate, the data cannot be used to read across from.

DR. LIEBLER: I think that's right.

DR. BELSITO: Okay. And what we are saying, is that for the isopropyl titanium triisostearate and titanium isostearate, what we need is a 28-day dermal. And if absorbed, other toxicity endpoints may be needed. And we needed a mammalian genotox to clear those two.

For the titanium citrate, we have method of manufacture, but we don't have impurities. So, we need impurities. We need concentration of use in cosmetic products. And we need, I presume, a 28-day dermal. And if absorbed, genotox endpoints. And sensitization at maximum concentration of use.

For the ethoxide and the salicylate, we need all of those plus method of manufacture.

DR. LIEBLER: Correct. We need method of manufacture and impurities for all of them.

DR. BELSITO: Well, we have method of manufacture for citrate.

DR. LIEBLER: Right. Exactly.

MS. FIUME: Dr. Liebler, when you say for all of them, does that include the isostearate and --

DR. BELSITO: No, no.

MS. FIUME: -- triisostearate.

DR. BELSITO: No. The triisostearate, we need a 28-day dermal. And if absorbed, other toxicity endpoints. And we need a mammalian genotox. That's all we need for the triisostearate and the isostearate.

MS. FIUME: Because this was an IDA, I believe it said the impurities data that were received were okay, but not ideal. Do you want that to be part of that request; or it passes for the purposes of the report?

DR. LIEBLER: Actually, I take that back. It's fine. I mean, the real impurity issue is going to be metals. And we've got test data that says the following metals were not detected.

And I should point out that in Wave 2 we do have method of manufacture for the triisostearate, isopropyl titanium triisostearate. So, I think we're good there.

DR. BELSITO: Yeah. So that's why we're only asking for 28-day dermal and the mammalian genotox for the triisostearate and the isostearate.

DR. LIEBLER: Yup.

DR. BELSITO: And for the titanium citrate, we have method of manufacture; we don't have impurities. So, we're asking for impurities, 28-day dermal tox, if absorbed other endpoints, use concentration in cosmetics, and sensitization irritation at concentration of use. And for the other two we need method of manufacture plus all of those.

DR. LIEBLER: Correct.

DR. BELSITO: Sorry, I'm a slow typist. Okay, anything else on these titanium ingredients?

Day 1 of the June 4-5, 2018 CIR Expert Panel Meeting – Dr. Marks'Team

Titanium Complexes

DR. MARKS: Okay, let's see next is organo-titanium ingredients. I'm getting the sense my team is tired.

DR. HILL: No, I'm doing fine.

DR. MARKS: Good.

DR. HILL: When the coffee wears off I'm toast.

DR. MARKS: Super. This is a draft report; so, this is the first time we review these five organo-titanium ingredients. And of course, Tom and Ron, the first question is, are these five organo-titanium ingredients -- all five of them, do you like them put together the way they are?

DR. HILL: I'm getting there.

DR. MARKS: And then the second question, of course, is what do we need?

DR. HILLS: First of all, they're misnamed; so, can we start with that. These are not organo-titanium compounds.

DR. MARKS: Yeah, citrate, salicylate, yeah. Well, we let you and Bart --

DR. HELDRETH: Yeah, what name would you like?

DR. MARKS: Exactly.

DR. HILL: I can tell you as soon as I get there, because I'm pretty sure I wrote down what I thought they ought to be. They're not organo-titanium because, by definition, an organo-titanium would have a carbon-titanium bond, which is possible, but that's not what we're seeing here. And I also suggested that we remove the citrate. And I think there was one more.

DR. MARKS: Let's get back to --

DR. HILL: I'm trying to find the table that has the ingredients listed, so I know which ones I was suggesting.

DR. SHANK: Page 5.

DR. MARKS: Yes.

DR. HILL: Either page 5 or I dropped down one page.

DR. MARKS: I have page 19. Oh no, that's the uses. Yeah, page 5 is the one that has the --

DR. HILL: Yeah. It was someplace else I marked them, but this is okay.

DR. MARKS: The data profile?

DR. HILL: Yeah, so I suggested that titanium salicylate get gone but go in our salicylates report, which we haven't gotten to yet. There's no reason not to do that. And it doesn't belong here. And citrate be gone because that's just a salt. So, if we just have carboxylic with titanium, those are really just salts.

But when you have the titanium oxygen bridge to an alcoholic OH, like you do in titanium methoxide where we have four ethers linked or actually in the case of isopropyl titanium triisostearate, you got the isopropyl oxygen directly linked to the titanium. And then basically OH groups that are esterified with stearates.

I think I suggested something to do with titanium tetraethoxide. I know I have this. Anyway, the name doesn't, at this point, matter. We can hash that out later.

DR. MARKS: Well no, I think it's important.

DR. HILL: But it did go to -- I doubted that the search strategy captured, necessarily, everything that we wanted based on --

DR. MARKS: Well, we'll see what we need. I think that's -- let's get back to the ingredients.

DR. HILL: Well, it's important because the dictionary name is wrong. When they say, titanium triisostearate, that's a screwed-up name.

And that's part of the problem here. And it's actually not isopropyl titanium, it's isopropyloxy titanium, trioxide, triisostearate. So, the names is a mess, and that kind of screws up the chemistry class.

DR. HELDRETH: For the isopropyl titanium triisostearate, I'm sure Wilbur used that CAS number.

DR. HILL: Well, I know. And that will catch anything that has a CAS number in it. SciFinder, if you search by CAS number, will not pick up anything in PubMed that doesn't have the CAS number associated with it, unless they've changed that recently.

And definitely, most PubMed articles don't come with CAS numbers attached to chemicals that are in them. I'm not sure about TOXNET, they probably do most of the time, but I'm not sure. So, you need to

look about that.

DR. HELDRETH: My understanding, though, is that when you use SciFinder, and you put in a CAS number, before it searches through the articles, it finds the CAS file, which has the known names that are associated with that CAS number. And when it searches through the literature, it uses that CAS file.

DR. HILL: If it does, that's a change from several years ago where it didn't. So, if it does, that's great, then we have better confidence. It wasn't doing that until fairly recently if that's the case.

DR. HELDRETH: That's how it was explained to me by the person that trained us.

DR. HILL: Okay, great. Then they did do that. I always thought they should and I hoped they would, but -- okay great, so that helps me. Yeah, so then I think I suggested look at what the synonym names are listed in chemical abstracts and go from there.

But I thought this should be just down to two ingredients, maybe three ingredients. I think the isostearate, the ethoxide, and the isopropyl titanium triisostearate. I though those were fine. But then the other two should go because they're just carboxylic acid salts. And the salicylate could go to there. And I'm not sure about the citrate.

And the reason that's important, is because citrate gives you a soluble form you can study titanium uptake, but there should be nothing about the trafficking of titanium citrate that's in common with these other guys, in terms of -- I know Dan hates this word -- but, bio-handling. I don't think titanium ion has any strong toxicities that are worrisome.

DR. MARKS: So, back to the ingredients; we'll get to the name in a minute, back to that. But Ron Shank, Tom, any problems deleting the titanium citrate and the titanium salicylate? I understand your reasoning for the titanium salicylate, we do have a salicylate coming up still to review. And then the citrate, you just didn't think it belonged in this group.

DR. HILL: No. It's very disparate from your isopropyloxy triester and the titanium tetraoxide tetrastearate, basically. Tetraisostearate.

DR. MARKS: That's a chemistry issue. Ron Shank, or Tom, any comments about that?

DR. SHANK: No.

DR. MARKS: So, the three ingredients that we would be reviewing in this report would be the isopropyl titanium triisostearate, titanium ethoxide and a titanium isostearates. Okay?

DR. SLAGA: Okay.

DR. HILL: And the structures are given on page 18 and 19, in case anybody needs to look. As far as I can see they're correct.

DR. MARKS: So, you don't like organo-titanium ingredients. What would you suggest?

DR. HILL: I wrote something here. I was still trying to find what I thought, but maybe -- I might have weaseled a little on this and suggested that you look at what SciFinder had for that isopropyloxy stearate. And I think it's going to be named as a titanium tetraoxide derivative.

But that, like I said, is sort of in a side -- what's much more important is the chemical similarities in terms of assessing safety. And in this report, most of the systemic data is for delivering that citrate.

But what I wrote down here, is the titanium oxygen bond is much more like the aluminum oxygen bond in alumina than the sodium oxygen bonds in sodium hydroxide. Or like the sodium oxygen bond in sodium acetate. So that's the thing. Those are much tighter, much more covalent-type bonds when you have an alcohol involved than a carboxylate salt.

DR. MARKS: Okay. So, what are the needs we have? The only one being used, if I have the use table correct, is the isopropyl titanium triisostearate. Is that correct? Over 500 uses, 573 with a 1.5 percent concentration on leave-on. The others aren't used.

DR. ANSELL: So at least that one remained in the family.

DR. HILL: Yeah.

DR. MARKS: Yes. Exactly. Family of three, it's decreased in size from five.

DR. HILL: My need on that, what I wrote was, an impurities profile or an alternative, might be a specification sheet from known vendors. Or another alternative might be method of manufacture, enough to give some idea about potential impurities. Of course, we usually don't list our needs that way, but.

DR. MARKS: Method of manufacture, impurities --

DR. HILL: And impurities is our standard request, yeah.

DR. MARKS: Okay.

DR. HILL: Use concentrations are low, but we really need dermal penetration information. And what I wrote was dermal bio-handling, by which I mean what happens to this stuff in the skin. I'm not worried about systemic exposure because the use concentrations are quite low.

And if not available, search other possible proxy substances that might be -- such as titanium tetraoxide, mono up to tetraether with at least one of the four groups being a long-chain acyl. So, we have isostearoyl, some other long-chain acyl. In other words, a fatty acid moiety.

So, if we can see that goes to -- I would just put the structure in with titanium linked to four oxygen and see what all pops up. And see if you can find some proxys. And I'm saying you, meaning Wilbur, because the citrate doesn't work for me.

DR. MARKS: There's not a lot of data on this compound.

DR. HILL: No, there's not.

DR. MARKS: So, do we need data on 28-day dermal tox on this, do you think, and go from there? And then do we need -- we don't have anything on genotoxic or carcinogenicity.

DR. SLAGA: Well, we have genotox in Wave 2.

DR. MARKS: Oh, okay. Why didn't I have that.

DR. SLAGA: And we had irritation sensitization data there.

DR. MARKS: Here's Wave 2. Oh yes, okay. There's definition chemical properties. That's why I didn't have them listed.

DR. HILL: I knew they were somewhere.

DR. MARKS: Yeah, method of manufacture, impurities analysis. So, we have a lot of stuff on it. That's why I didn't have it listed. I think I put in here safe, yeah. We really don't -- Wave 2 should address all this stuff.

DR. SLAGA: I don't think it was method of manufacture and impurities related to the --

DR. MARKS: It says -- here it is.

DR. ANSELL: Yeah, I don't have the Wave 2, but it says in my summary that Wave 2 will contain method of manufacture, physiochemical properties, metal analysis of the titanium, and summaries of acute oral, dermal, ocular and genotox.

DR. MARKS: Yeah, that's from May 23rd, wave 2. Yes, Jay, I have the same. I'd go back and look at it, but it looks like we have all the needs. The sensitization data is good. It's not an irritant. It's not a sensitizer. And then I guess, you say, the isopropyl basically represents the other two, the oxide and the isostearate.

DR. HILL: I was a little uncomfortable reading across to the ethoxide. And I wondered if we did pick up all the information based on the way the searching was done. But we had a CAS number, so. But it's hard for me to believe there isn't some more tox data out for that substance than what we've got.

So, my request was put that substance in, find the chemical synonyms that pop up in chemical abstracts, and make sure we search those by text in the other databases and see what you can come up with.

Although I would think, any studies that have been done on that, if you search it by CAS number and it is in fact using those synonyms, that should catch anything that's in the open regular literature. I saw Wilbur came in.

DR. HELDRETH: I can run a structure search just to make sure that that's not something that --

DR. HILL: I didn't know if we had that capability or not. But if we -- okay, great.

DR. HELDRETH: Yes. I can run structure search in SciFinder and just put our groups out there.

DR. HILL: Technically, when I log onto SciFinder, I'm supposed to sort of hit the link that says I'm not doing the search for anything other than academic. And I'm not sure they count this.

DR. HELDRETH: I'll run a structure search just to back up and make sure we captured it all.

DR. HILL: It's irritating, but that money is what keeps them in business.

DR. MARKS: I think we can move forward as safe with the isopropyl titanium triisostearate with wave 2 data. We basically got all those things filled in. But the ethoxide and the isostearate, you wouldn't feel comfortable reading across?

DR. HILL: No, I don't.

DR. MARKS: And it's unlikely we're going to get -- those are not being used, is that correct?

MR. JOHNSON: Correct.

DR. MARKS: So, it's unlikely we're going to get any data on it. Do we do a split conclusion of this; safe for the isopropyl titanium triisostearate and insufficient data for the ethoxide and the isostearate?

DR. HELDRETH: If you'll have insufficiencies, this is the draft report stage --

DR. MARKS: Yeah, it will be an ISA announcement, yeah.

DR. HELDRETH: -- we'll put an IDA out, yeah.

DR. MARKS: Insufficient Data Announcement, yeah.

DR. ANSELL: I would argue since this is a first review --

DR. SLAGA: Let's try it.

DR. ANSELL: -- that the family has been ill formed. And that these two materials should not have been included because you cannot rely on the data on those three to draw any conclusions. And therefore, they should be removed and put in their own report. Otherwise we're just going to drag these along to every meeting and say, well the data's not there.

DR. MARKS: Oh no, we had the data for isopropyl.

DR. SLAGA: The other two.

DR. ANSELL: No, no. The two that were --

DR. MARKS: Yeah, the other.

DR. ANSELL: We don't need a split decision. We need to conclude that the family is just three members, it's not five members.

DR. MARKS: Oh yeah, we've already made a decision it's only three members. Where I'm at, is can the other two -- which we don't have much data on, the ethoxide and the isostearate -- can we read across to that. Or do we say insufficient data announcement and just flag those two ingredients, which we need a lot of data on.

And that's probably where -- but we can get the heads up, we feel it's going to be safe for the isopropyl titanium triisostearate. So that's sort of where I'm going, but Tom, Ron and Ron, does that --

DR. SHANK: Well, for the three, I'd start with dermal penetration.

DR. MARKS: Yeah, okay.

DR. SHANK: You have systemic data, some, for the isopropyl titanium triisostearate. Still need reproductive developmental if it's absorbed.

DR. MARKS: Let me see.

DR. HILL: We've just got acute dermal toxicity and acute oral, but with a huge LD50, but it's acute. So, there's nothing chronic.

DR. MARKS: Right. We don't have reproductive.

DR. SHANK: For genotox you have one Ames assay.

DR. MARKS: Yes.

DR. SHANK: That's not enough to cover mutagenesis. So, I would start with dermal penetration. If they penetrate, then you need the systemic toxicity.

DR. HILL: And what I think will pop out is one, or probably all, of the triisostearate moieties will be clipped off in the skin before it gets anywhere. You won't see systemic uptake. But that's just a conjecture at this point.

DR. MARKS: Okay. That's for all of them, the dermal penetration, if yes, systemic toxicity.

DR. SHANK: Yes. Well, we have some -- yes.

DR. MARKS: Yeah. If we have some -- we have some already.

DR. SHANK: We have a little bit of data --

DR. MARKS: On the isopropyl.

DR. SHANK: Yes.

DR. MARKS: And then the other thing is you also want more genotox or mutagenicity for all of them?

DR. SHANK: Well, I would start with dermal penetration.

DR. MARKS: Okay.

DR. SHANK: And see what we get.

DR. MARKS: Is that the only need? At this point.

DR. SHANK: Well, that's the only need at this point.

DR. MARKS: Right.

DR. SHANK: If they penetrate, go into the circulation, then we need more.

DR. MARKS: Do we need irritation sensitization on the ethoxide and the isostearate? And again, these aren't being used so it's not like we're going to get it.

DR. ANSELL: With less emphasis, I kind of make the same argument of, if the ethoxide is so different from the stearate that we can't rely on any of the data, why are we reviewing these as a common family? Each of them should, in their own way, inform a decision about all the other members of the family.

DR. HILL: I can answer that question, at least, for the isostearate now however, because this is what it says about the isopropyl titanium triisostearate. Product is predominantly titanium, substituted with one isopropoxy and three isostearate ligands. However, it will also contain the tetraisostearate and the diisopropoxy/diisostearate titanates as well.

So, it's actually a mixture. It doesn't give us the exact percentages typical of the production

process. But basically, that isostearate that's in there is as an ingredient, is contained in what sounds like appreciable levels in the product that has data.

DR. HELDRETH: And read across is not the only rationale for grouping. It's a great one, probably the best one. But if there's other things in common, like how these things are manufactured or the residual impurities that will be part of the process, those are rationales for keeping things in a group as well.

DR. ANSELL: And is that true of the ethoxide and the isostearates?

DR. HILL: So, the isostearate, like I say, that is effectively present as a substantial component of the other product.

DR. ANSELL: No, I think that makes a lot of sense.

DR. HILL: The ethoxy -- that's a gray area to me. I think it might be --

DR. ANSELL: Well, we're just lining ourselves up at stage one, for carrying through a material that no one's using and there's very little interest. And cannot rely on any of the data on the materials that we are interested in and carry that through every single report and have a discussion at every single meeting.

DR. HELDRETH: But as was said, earlier today, you can't rely on the VCRP to determine whether or not something is in use or not. It is a voluntary program.

And so, keeping or eliminating an ingredient on our priorities, or reviewing in a document, should not be based on the VCRP. That's why we go after ingredients that are in the dictionary as potential ingredients, at the very least, even when we don't have the VCRP saying that it's in high use.

DR. ANSELL: And that makes sense when we can rely on the data on one to inform decisions about larger families. It doesn't argue that we should put in anything with titanium and find ourselves in a situation where there are two materials, which are highly related manufacture that are present as potential raw materials. And then a third material, which is related only by virtue of the titanium.

If there was a justification, as you said, then let's make that argument. And I would not argue that its presence in the VCRP argues that the material should be concluded to be safe. Right, I would not say just because it's there, at zero uses, that that makes any argument as it relates to safety. But I do think it makes an argument about where we should be spending our time and energy.

MR. JOHNSON: I have one question. Are the data on isopropyl titanium triisostearate relevant to safety evaluation of titanium isostearates?

DR. HILL: Well, this is what I'm saying; is they say the titanium isostearate is actually present as a significant fraction of that isopropoxy ingredient. That's what you've got in Wave 2, page 11. So, from that point of view we still can argue with the read across because they're not telling us what portion typically. It would nice to have that. So, if we knew it was 1/4, then if we had safety data that said at 10 percent that isopropoxy one was good, then that would suggest that at 2.5 percent that other one just fine, most likely. I'm not sure if that fully answered your question.

MR. JOHNSON: So, we need the dermal penetration data on the titanium isostearates?

DR. SHANK: Yes.

DR. HILL: Or we could probably read across from that isopropoxy one, because we will find out if the stearate -- if we find out if the stearate esters are cleaved off, as I would suspect in skin, if it happens for that, it's going to happen for that other one for sure. It will be carboxylesterase is in the skin to deal with lipid structures. Of course, that's the skin route. So that doesn't -- incidental ingestion it might not apply.

DR. MARKS: So, let's get back to -- and taking Jay's comments into consideration here. So, we had been narrowing it down to three ingredients, the isopropyl titanium triisostearate, the titanium ethoxide and the titanium isostearate. We want to keep those three. Or do we want to, based on Jay's comments, just limit it to the one that has over 500 uses, the isopropyl compound.

DR. HILL: I suppose I have an unusual -- and I'm not sure the tabling report is what we want to do when we could keep it moving forward. But I would like to see the result of Bart's search, because he might actually turn up, if he does a structure base search, titanium tetraethoxide, he might turn up data for that ingredient that we don't appear to have any data on if we get the right --

DR. MARKS: Yeah, we don't have to table it. We can do an insufficient data announcement.

DR. HILLS: Right. Or something similar enough.

DR. SLAGA: This is early so.

DR. MARKS: Yeah. But for our team, moving forward, do you like those three ingredients, at least, at this point?

DR. SLAGA: Seem okay to me.

DR. MARKS: Ron Shank?

DR. SHANK: Like is a strong word, but I accept.

DR. MARKS: What would you prefer?

DR. SHANK: Accept.

DR. MARKS: Yeah, okay.

DR. SLAGA: Or we just limit and just stick to the isopropyl and get rid of the rest.

DR. MARKS: Well, I think we're in the same as the PTFE. And we danced around the head of the pin for a while and then came to the conclusion for our team that we limit it to one. We can do the same for this.

I think the three were based on chemically what you felt were related and you eliminated the others. This one we're eliminating the ethoxide if we were to do it, and the isostearate just because they're not being used, and we aren't going to have data on it.

DR. HILL: I think we keep the isostearate.

DR. ANSELL: No, no. I'm not recommending it for that reason.

DR. MARKS: Okay.

DR. ANSELL: I'm recommending it because Ron has come through and asked a whole series of questions about the ethoxylate, which have already been responded to for the isostearates. So, it suggests to me that they are not sufficiently related to be carried forward together.

DR. SLAGA: Yeah.

DR. ANSELL: And that the ethoxylate should be removed and put into its own report, which is unlikely to happen because it's not used. But it's not because it's not used, it's because we already, in the very first report, divided them into two separate families. Two that we're talking about with one set of data; and one we're talking about with a whole different set of data requirements.

DR. HELDRETH: And then alternatively, instead of just deleting ingredients at will, the panel has already done the work. The writer has already done the work to look at these ingredients. If we're confident that if we put out an insufficient data announcement we're going to get nothing, then we won't have to do any more work on these two ingredients, if we continue the insufficient data conclusion to finality.

DR. HILL: And then you just have two ingredients that are insufficient data and that's the deal.

DR. HELDRETH: Right. And then ultimately, they both will go on our zero-use list. And that puts notice out to anybody that would choose to use those ingredients, in the future, that there's not enough data out there to support their safety.

DR. HILL: So, that's the approach I would like to see happen. I'll just go on record as saying in that case --

DR. MARKS: Just two ingredients?

DR. HILL: Three. Three.

DR. MARKS: Still three.

DR. HILL: And the other reason is because if you take that isopropoxy that they've already stated at least some percentage of that has two isopropoxy groups. If you cleave the esters off the other two, you've got two isopropoxy and two free OHs, which I think will be basically T -- it will be a single oxygen. What will happen is you'll eliminate water.

I would predict that ethoxy will be metabolized to similar and be the diethoxy in that particular case.

DR. SLAGA: Yeah, but we don't know that for sure.

DR. HILL: We don't know, but I'm still saying the literature search hasn't been done right yet. So, we won't know that until we finish the search again. And then once we have a structured-based search, and we find out what is or isn't out there, we will be in a position to make a better decision about this.

But I don't see any downsize, from where I sit, of putting that on zero -- so, we have no data, but it's in the dictionary, it's on our zero-use list where we don't have any supporting data. What's the downsize? Other than we have one more ingredient that's not --

DR. ANSELL: It under minds the definition of insufficiency; and chews up a lot of time that would be better served on materials of interest.

DR. HILL: But it's in the dictionary.

DR. HELDRETH: That's a mischaracterization completely. The CIR steering committee met, in 2009, with the intention of adding these new categories. And zero use was one of the ones that they set up for such a purpose as when we have ingredients before us, that we're reviewing, and they're not in use.

We know that the VCRP is voluntary. Not everybody reports to it. We see it constantly in our reports where we'll either have the VCRP saying nobody's using it, and we have a concentration of use from a survey or vice versa. So, we know that these are not things that we should be relying on.

DR. ANSELL: And again, it's not based on they're not being used; it's based on the fact that we can't look at them as a family. That we have two materials which everyone is having one conversation, and a second material that is having a completely different conversation. And I don't think they should be in the same report.

And that's just my comment, that we've been making throughout the day, where we've had a series of material this morning and will continue to come up; which have gotten carried through and are distracting and detracting from the focus on materials of interest.

DR. HILL: I'll just go on record as saying the ethoxide is chemically related enough that we could consider carrying it through for one more round, while we see if there's anything more to be had from the search. Because I think there will turn up something, if you do the search and pick some additional potential compounds.

And if we determine that the chemistry tells us that these shouldn't be grouped together, in the next round, then we divorce it and decide what to do about it that point. I don't think it should be kept together just administratively because there's a titanium there. If we determine that they're chemically disparate enough, then we have the rationale for dropping them in the next round, and I think that'd be okay too.

I think there's going to be more information there in the literature because titanium chemistry's been out there for a while. Titanium oxide ethers have been out there for a while. I think some other things are going to turn up if you expand your search a bit.

And then whatever you turn up, you can decide what should go in this report. Because we really are missing a lot of data on the lead ingredient anyway, so that's going to be insufficient as well, unless we get some more information.

DR. MARKS: So, to move forward, I think, tomorrow I'm going to move that we issue an insufficient data announcement. That they're going to be three ingredients, the isopropyl, the titanium ethoxide and the titanium isostearate.

And when it comes up to the reasons why, I'm going to say, Ron Hill, why don't you talk about the chemistry. Why you like these three. And then I'm going to say the insufficient data need is dermal penetration. And I'll ask Ron, maybe, to clarify that, if that sounds good. Does that sound good?

DR. SLAGA: Okay. It does to me.

DR. MARKS: Does that sound acceptable?

MR. JOHNSON: Which three are safe?

DR. MARKS: It's the isopropyl tri --

DR. HILL: Not safe. Kept.

DR. MARKS: -- triisostearate. The titanium -- and that's the one that has all the uses at a max concentration of 1.5 percent, we have sensitization on that. I know you sent a lot of stuff in the Wave 2, Wilbur, but still Ron Shank wants to see dermal penetration of these to make sure there's not systemic toxicity. If there's penetration, then we need more systemic tox and more actually mutagenicity/carcinogenicity.

DR. SHANK: Correct.

DR. MARKS: So, you have the triisostearate, the ethoxide and the isostearate. You have those three? The first one, the third and the fourth one. What will be eliminated is the citrate because it's chemically not similar. And Ron Shank suggested the salicylate be added to the upcoming salicylate report.

Okay. Any other comments? Oh, that was a -- we'll see what happens tomorrow. I think it'll be perhaps equally as --

DR. SLAGA: Oh dear.

DR. MARKS: Huh?

DR. SLAGA: I better get a later flight.

DR. MARKS: We're still in the beginning stages of this. And next one, and we didn't even settle for the name. I'm going to continue calling it organo-titanium. Or do you want me to just call it titanium ingredients tomorrow?

DR. HILL: If you want to stick with organo-titanium for now, that's what the title is for now, and then it can be fixed.

Day 2 of the June 4-5, 2018 CIR Expert Panel Meeting - Full Panel

Titanium Complexes

DR. MARKS: The first thing with that -- while I pull it open -- was we had quite a bit of discussion in terms of what the title should be. We didn't get any better ideas, but at any rate just to put that out. Ron Hill particularly didn't like the Organo part of it.

Our team looked at these five ingredients. This was the first time we've seen this, so the first time for review. We felt that we wanted to move that an insufficient data announcement be given. We reviewed just three ingredients in this report, the isopropyl titanium triisostearate, the titanium ethoxide, and the titanium isostearate.

We wanted to remove the citrate, because chemically Ron Hill, I think, didn't feel the chemistry supported putting it in this group. And then the titanium salicylate would go to the salicylate report, so you'll hear that ingredient again later on.

What we needed was dermal penetration of these ingredients; and if there was, then, systemic toxicity. So, the motion is insufficient data announcement.

DR. BERGFELD: With those specific comments --

DR. MARKS: With those comments, sort of giving -- I know we probably don't have to agree on the ingredients today with the insufficient data announcement; but I think we should, going forward, if we need dermal penetration, it would be for the ingredients we're going to include in this report.

DR. BERGFELD: Any comments about the ingredients to be included in the report, since I did not hear a second? Dan?

DR. HILL: One thing I will say is we had a very protracted discussion of the chemistry yesterday, and then I went back and reminded myself of what I thought I did and didn't know. And there're some interesting things that popped out of that, like that tetraethoxy compound, if you put it in water there's a five-minute half-life. So, it's interesting what if anything -- I can only envision that in some very specialized uses, which appears we might not be using right now.

But it raises some issues about the chemistry of that isopropyl titanium triisostearate, which is not named very well; but it raises some questions about that as well.

And the nature of the bond between a carboxylate and titanium, which there's a fairly recent paper that I stumbled on last night, dealing with the speciation of the citrates complexes with titanium; which suggested we need some further information about the chemistry, which is not part of this motion and second process, but just I still think it's those three ingredients. But I wonder why the ethoxy stays in as well.

DR. LIEBLER: I felt that since these were in the dictionary, they were brought to us for the report, at this point we'd keep them all in and we'd say what were insufficient for. And there're obviously some interesting issues; with respect to chemistry they're going to vary somewhat on probably dermal penetration, but we need data. So, anyway, that's, I think, pretty consistent with what I think we talked about yesterday.

DR. BERGFELD: Don, you want to comment?

DR. BELSITO: When I looked at these I didn't see the grouping at all. And I'll leave that to Dan to duke it out with what the Marks team wants to do. I also mentioned the potential of moving the titanium salicylate to the salicylate report but was told that that is quite different than the salicylates that we are looking at.

DR. HILL: I disagree with that.

DR. BERGFELD: Okay.

DR. BELSITO: Would whoever brought that up, in terms of a bonding or the nature of the titanium salicylate, respond as to --

DR. BERGFELD: Dan, do you want to respond?

DR. LIEBLER: Yeah, I thought that the driver of the biology, biological interactions, if any, would more likely be the titanium and the salicylate. So, I think this ingredient belongs in this report, not the salicylate report.

DR. BERGFELD: It seems that keeping it in an insufficient data announcement, one could keep all these ingredients for the time being.

DR. LIEBLER: Correct.

DR. BERGFELD: And then look at this chemistry and accept later.

DR. HILL: Can we put that ingredient in both reports? I know that's something we've really never done, probably not. But I agree that there may be a toxicology issue with the titanium itself. There's no report of use of the titanium salicylate, except that it appears there might be a lot of informal compounding use of it

being done out there.

DR. LIEBLER: We've created enough complications this morning; let's keep it in the report.

DR. HILL: I still think it should go to the salicylate report, but that's just me.

DR. BERGFELD: I think that can be resolved later.

DR. HELDRETH: If we get any data on that specific ingredient, certainly the data can go in both reports. And then the Panel can determine if it's useful in either one.

DR. BERGFELD: Oh, so it can be crossed referenced.

DR. HILL: And I kind of like to know if FDA is looking at this whatsoever, so maybe we can investigate that.

DR. BERGFELD: What do you mean?

DR. HILL: I wonder if that compound is on FDA's radar, given that there does appears to be a fair amount of extemporaneous compounding of that compound for use out there in the world. I don't know if it's in the United States or not though.

DR. BELSITO: The compound is titanium salicylate?

DR. HILL: titanium salicylate, which is interesting because you didn't dreg up any data so far. And I don't know if that's because it was ignored, if it's anything that look like drug use; so, Wilbur, did you find any information on that compound at all in terms of biological -- the titanium salicylate?

MR. JOHNSON: No, I did not.

DR. HILL: Okay.

DR. BERGFELD: Okay. Don, did you want to make a comment?

DR. BELSITO: Again, I will let Dan duke it out with the other team in terms of whether we drop any of these from this report, because to me they all look quite different. However, I would point out that the only one that's in use is the triisostearate; and it's the only one that we have some data on.

We have method of manufacture. We have impurities. We have some tox data. We have some in vitro genotox data. But even that would still be insufficient for a 28-day dermal, and if absorbed, other endpoints toxicologically, and also mammalian genotox, which we don't have.

So, if these other ingredients are, I mean, we can lump them, but I think what will end up happening is they'll all be insufficient because they're not used. We're not going to know concentration of use. We're not going to know anything about them. So, I really don't care one way or the other.

DR. BERGFELD: But at this point we do not know any of that?

DR. BELSITO: Right. We don't know any of that.

DR. BERGFELD: Ron Hill?

DR. HILL: I'm going to do what we would call crawfishing, where I currently live, which is say keep it in this report. I'm going to go back on what I just said about salicylates, mainly because there is some chemistry information out there in the literature, and it could possibly inform this other.

And in the information we got for the isopropyl triisostearate, there's not information given to us about delivery vehicles that were used in the toxicology study, and given the hydrolytic instability of the tetraethoxy and -- actually tetraisopropoxy, where if it sees water down the street it's not going to hang around very long. I think that information is important.

And there's certainly chemistry information about the citrate; and by keeping it in we might be able to capture as well, to inform reviews of whatever ultimately we can't act on. So, I'm crawfishing; I'm changing what I said earlier and saying let's keep them in --

DR. BERGFELD: Okay.

DR. HILL: -- until we get the titanium oxygen bonding chemistry and stability of these complexes, and hydrolytic stability and all that, and then go from there.

DR. BERGFELD: So, you've made a motion, Dr. Marks?

DR. MARKS: Yeah.

DR. BERGFELD: And did you isolate those to three ingredients, or did you keep everything? I've forgotten now.

DR. MARKS: No. The motion was to put forth an insufficient data announcement, and that's not changed. I think the five ingredients are really fine. Would leave it at that. I don't know that we need to make a final decision on that, but it sounds like we're getting closer to keep all five.

DR. BERGFELD: Okay. Is there a second?

DR. BELSITO: Second to keeping all five; and the insufficiency for the triisostearate is 28-day dermal, and if absorbed, other toxicologic endpoints and mammalian genotox, correct?

DR. MARKS: Yeah.

DR. BELSITO: And then for the others it's literally everything, concentration of use, method of manufacture, impurities, 28-day dermal, mammalian and in vitro genotox, sensitization, irritation, and concentration of use, the whole nine yards.

DR. BERGFELD: Fine. Any other discussion? Otherwise, I'll call to question. All those in favor of this going insufficient? Thank -- yes?

MR. JOHNSON: I didn't mention this, but during the polyfluorinated polymers review, we didn't talk about EPA's limitation on two impurities; and that the staff will be calculating a value that would indicate that there would be no concern about the safety of those.

DR. BERGFELD: Okay. Will that be recorded in the minutes and then we'll act on that? But this is unanimous vote on this ingredient. We're moving forward to the VP Polymers, Dr. Belsito.

Day 1 of the September 24-25, 2018 CIR Expert Panel Meeting – Dr. Belsito's Team

Titanium Complexes

DR. BELSITO: Okay. Titanium complexes. At the June meeting, an insufficient data announcement was issued for isopropyl titanium triisostearate, 28-day dermal tox. Depending upon those results, addition systemic tox and mammalian genotoxicity. And we got 2 percent isopropyl titanium triisostearate with black iron oxide, acute oral toxicity, skin irritation, ocular irritation, but we did not get what we requested.

We also requested use concentration data, manufacture and impurities, 28-day dermal, skin sensitization and irritation on the citrate, ethoxide, isostearates and salicylates. And we didn't get any data on that. Correct?

DR. LIEBLER: Right. We have the same data needs still.

DR. BELSITO: Right.

DR. LIEBLER: I think we are still where we were. Yeah, we're on our way to being insufficient for everything.

DR. BELSITO: Well, we do have data on triisostearate and citrate. No?

DR. LIEBLER: I meant that we don't have our data needs met completely for any of the ingredients.

DR. BELSITO: Right.

DR. ANSELL: But we would suggest that perhaps the isopropyl titanium triisostearate we do.

DR. LIEBLER: You have 28-day dermal?

DR. ANSELL: No. But we have genotox. We have acute ocular dermal --

DR. LIEBLER: You have mammalian genotox.

DR. ANSELL: -- sensitization and an application, which shows that it isn't actually -- there's no actual exposure to the material as such as it's a complex -- it's color coating, so it's complex to the colorant.

DR. LIEBLER: Is that a chemistry part that we don't have, Jay, that description of the chemistry?

MR. JOHNSON: It's in the unpublished data. PDF Page 40.

DR. LIEBLER: Forty?

MR. JOHNSON: Yes.

DR. LIEBLER: Oh, the sideways PDF PowerPoint presentation.

MR. JOHNSON: Yeah.

DR. LIEBLER: This isn't really incorporated in our text at this point?

MR. JOHNSON: No. Actually, the reaction is on page 41, I'm sorry.

DR. LIEBLER: Right.

DR. BELSITO: Where it, 41?

MR. JOHNSON: On page 41.

DR. BELSITO: Yeah.

MR. JOHNSON: Does this mean that there's no isopropyl triisostearate in the formulation?

DR. ANSELL: That the toxicity on iron oxide would be a better predictor of the toxicity. You know, it's a surface coated colorant. It's a surface coating for colorants.

MR. JOHNSON: What does the 1.5 percent use concentration refer to, you know, given that chemistry?

DR. ANSELL: I would have to ask what the dispersant is.

DR. LIEBLER: I think we really have a shortcoming in this report, with respect to an accurate description of what the chemical entities as used in cosmetic products are. These are represented as simply these coordinate complexes of, you know, like titanium ethoxide, isostearates, et cetera.

And this presentation of this as essentially a coating for a pigment, raises the question of what is the nature of the full molecular species on which the titanium isostearate is attached. And I don't know is that pigment a big molecule? Is it a little molecule? Do we know, Jay?

DR. ANSELL: It's titanium dioxide.

DR. LIEBLER: No. No. The pigment that it's attached to.

DR. ANSELL: Yes.

DR. LIEBLER: Oh, that's just titanium dioxide --

DR. ANSELL: With a surface coating.

DR. LIEBLER: -- with the titanium isostearate coating on it. But it's a titanium dioxide

particle?

DR. ANSELL: Right.

DR. LIEBLER: So that's not absorbed.

DR. ANSELL: Right.

DR. LIEBLER: Okay.

MR. JOHNSON: And it's bound to black iron oxide, is that right?

DR. ANSELL: I don't know about the black part.

DR. LIEBLER: I thought that was another thing.

DR. HELDRETH: The data on acute oral tox skin irritation was on a 2 percent isopropyl titanium triisostearate on black iron oxide.

DR. LIEBLER: So, that's yet another -- black iron oxide is another particle on which this stuff serves as a coating.

MR. JOHNSON: That's the pigment though, is it no?

DR. ANSELL: Right. That's my understand.

DR. LIEBLER: So, the black iron oxide is a pigment. The Titanium dioxide is a pigment. And then the titanium isostearates are coatings around the outside of the pigment, both of those.

DR. ANSELL: It's a surface treatment for the colorant.

DR. LIEBLER: See, that's not at all clear from the description of the chemistry. It sounds like we're just talking about titanium coordinate complexes sort of free floating by themselves. And those are then relatively small molecules. And then we think really differently about their absorption distribution and toxicity.

For example, if the form of use of these is just in this pigment coating, then I think the 28-day dermal goes away because there's no absorption.

DR. BELSITO: Do we know that?

DR. LIEBLER: Well, that's what I'm asking.

DR. ANSELL: Well, and that is our position, is that these are just surface coatings, they're not free material. It's very much like the hydrogen peroxide or hydrochloric acid discussion. It's kind of philosophical to call that a cosmetic ingredient when, you know, it's completely reacted or in this case --

DR. LIEBLER: But that's how it was presented to us.

DR. ANSELL: Yeah.

DR. KLAASSEN: And that has to be majorly stated, what's going on. What really is the chemical?

DR. HELDRETH: Right. There's no description of it as being part of this particle in the dictionary description. And we have no data or information to suggest that the other ingredients in this report are also on particles.

DR. ANSELL: Well, and we're not supporting the other ingredients.

MR. JOHNSON: So, does that mean that the data that we're providing on black iron oxide, with 2 percent isopropyl titanium triisostearate, cannot be used to evaluate the safety of isopropyl titanium triisostearate?

DR. ANSELL: It can be used to assess the safety of it as a cosmetic ingredient because it isn't used.

DR. BELSITO: But nowhere in this report does that say that that's how it functions.

DR. HELDRETH: Right. Because that's not what's described in the dictionary.

DR. BELSITO: Right.

MR. JOHNSON: Just a surface modifier.

DR. HELDRETH: This data submission was my first understanding --

DR. LIEBLER: We need to table this and re-derive, first of all, the description of the chemical entities, and confirm that. What is the chemical form of these? Because Table 1 just shows the titanium isostearate or citrate complexes as if they were just these low molecular weight molecules that were added to whatever cosmetic product. It doesn't make any mention of the fact that they're actually bound to these larger pigments. And that changes the way we would approach this entirely.

We need to essentially re-derive the chemistry section, the descriptions. These idealized structures really aren't relevant unless they're attached to something else. The molecular weights aren't informative, they're misleading.

DR. HELDRETH: But as far as we know that's only true for the isopropyl titanium triisostearate.

DR. ANSELL: Right. That's the only data we have.

DR. LIEBLER: Okay, and that's the one that's being used. I don't know if you have any

information in the dictionary as to whether or not the other ingredients that are listed are actually parts of some other complexes. The listing in the dictionary would tell you that, maybe?

DR. HELDRETH: It does not.

DR. LIEBLER: It doesn't tell you that.

DR. HELDRETH: And we've run across this same issue with other ingredients in the past where the dictionary is rather vague, but it leads you to believe it's just a small molecule. And then we find out, as we get information and process it, oh this was applied to a particle.

Now some of these other ingredients however, have functions that make it seem unlikely that they're used in that way. For example, titanium ethoxide is a binder.

DR. LIEBLER: Right. But that would leave those things all insufficient for the things we've already said they're insufficient for.

DR. HELDRETH: Right.

DR. LIEBLER: As long as they're in the report, and we don't have data, then they're insufficient for method of manufacture and composition, et cetera. And then you have a major correction for the isopropyl titanium triisostearate.

And I just want to know if there's any form of that that's just that molecule, not attached to a pigment. If there is any use for that, then we need to consider the 28-day dermal, et cetera. If the only form is the form that's attached to these larger pigment particles, then that dermal absorption issue completely goes away. And then we're really basically down to sensitization and irritation, things like that.

DR. BELSITO: Okay. So you're suggesting we table for clarification as to the true function of the --

DR. LIEBLER: The isopropyl titanium triisostearate.

DR. ANSELL: You know, we can discuss this tomorrow. But it went insufficient. We went out to the manufacturers and this is the answer we got back, is that it's used as a surface coating agent up to 1.5 percent. And I agree, absolutely, that that changes the types of data needs one would need to assess the safety of the material. But we have gotten no information back on any of the other materials and they should appropriately be carried forward with the insufficiency.

MR. JOHNSON: So, surface coating agent and surface modified are one in the same? Because the dictionary says surface modifier.

DR. HELDRETH: We've had a similar situation like this where we thought they were small molecules and found out in the process that it was actually a coating of the particle. And ultimately, what the panel concluded was safe when used as one of these coating things, and the data remained insufficient for all other uses.

DR. LIEBLER: I can't remember what it was. It was within the last year or so.

MR. JOHNSON: So, they're the same thing?

DR. ANSELL: I could not distinguish one from the other.

MR. JOHNSON: Okay.

DR. ANSELL: A coating versus a modifier.

DR. LIEBLER: So, in the irritation and sensitization section, as it's currently written we have -- on PDF Page 28, we have the yellow highlighted sentences under irritation which are the test results with the black iron oxide particle with apparently that coating. And that was no irritation in rabbits.

And then if you scroll down -- I'm sorry, at the bottom of that paragraph is a concealer containing isopropyl titanium triisostearate in an occlusive patch test with 23 human subject, no irritation. What I want to know is, is that stuff that was tested there, is that the pigment particle with this coating, or is that the isopropyl titanium triisostearate?

And then when you get to the next paragraph on sensitization I have the same question. What was tested? You have nonirritating, non-sensitizing, is that the pigment particle with the isopropyl titanium triisostearate?

I think we can't interpret the sensitization irritation data, or any of the other data for that matter, without some confirmation of what is the chemical nature of what was tested. The cosmetic ingredient was either a titanium dioxide or a black iron oxide with this coating on it. If it was, then I think we can take the data into consideration. If it wasn't then it doesn't represent the cosmetic ingredient that's in use.

DR. BELSITO: Right.

DR. LIEBLER: The reason I'm saying table it is that, I think, if we were to sit there tomorrow as a group -- I doubt this would happen -- but that we would make all these assumptions about what it is and how we can interpret the safety data and then go safe as used. I'm not there.

DR. KLAASSEN: Yes. Every time we mention this compound, in any experiment, we have to

say was it the pure compound or was it this coating.

DR. ANSELL: Yeah. I think I will check with -- as you guys -- but that's my assumption from our discussion, is that these were colored cosmetics in which this was used as a surface modifier. And that those concealers and colorants, and eye products, were actually compounded -- you know, compounded products which contained pigments, which had been surface coated, surface modified with this ingredient.

DR. KLAASSEN: Okay. We just need to be sure.

DR. ANSELL: Yeah. Yeah.

DR. KLAASSEN: That's all.

DR. ANSELL: And I'm hoping we can get that resolved tonight. We'll ask.

DR. BELSITO: Anything else on this one? It's 11:56, do we have time for vinylpyrrolidone polymers?

DR. LIEBLER: Let's have lunch.

DR. BELSITO: Let's have lunch?

DR. LIEBLER: Yeah. We got parabens and brown algae behind us. We have the wind at our backs.

Day 1 of the September 24-25, 2018 CIR Expert Panel Meeting – Dr. Marks' Team

Titanium Complexes

DR. MARKS: And I have the titanium complexes. At the June meeting, this year, the expert panel issued an insufficient data announcement with the following needs. And you can see those in Wilbur's memo dated August 29th. The isopropyl titanium triisostearate had 28-day tox, mammalian genotox. And then the citrate, the ethoxide, the isostearates and the titanium salicylate, we wanted four data points, use concentration, method of manufacture, impurities. Keeps coming up, Ron Shank, method of manufacture.

DR. SHANK: It's very important.

DR. MARKS: Yup. And 28-day dermal tox, skin irritation and sensitization. Let me see, I don't see that we -- we didn't receive any of the data. Oh, black iron oxide was received in response to the announcement.

DR. EISENMANN: What has become clear, since the last meeting, is the titanium isopropyl -- the isostearate one, the only use is a surface modifier. There's no other uses. You could do a conclusion like you did in the past, for one of these other ingredients. For that one ingredient say, for use as a surface modifier, insufficient data for the other uses. Because you still don't have the 28-day dermal or the mammalian genotoxicity.

We also are not sure that these ingredients all should be in the same report. Because that has that specific use, the other ones have completely different uses and have no uses. Anyway, have no -- I should say other functions.

DR. SHANK: What is a surface modifier?

DR. EISENMANN: They actually provide -- there's some slides at the end where they show the reaction of them. They attach it to pigment to modify the surface so it could dissolve better. And that's probably the main function, so it could be actually incorporated into the cosmetic product better.

DR. HILL: It would confer a hydrophobic surface and be very tightly bound, I presume.

DR. MARKS: Carol, which one is that again that's just the surface modifier?

DR. EISENMANN: The one that's used.

DR. HILL: The triisostearate.

DR. EISENMANN: Isopropyl titanium triisostearate.

DR. MARKS: Okay. So, it's the first one listed here.

MR. JOHNSON: And I'd like to call the panel's attention to PDF Page 41, that has the reaction, you know, sequence for that.

DR. HILL: If it does, I missed that. I missed that. Yeah. That's how I expected it would go.

DR. MARKS: You're saying, Carol, then because it's only a surface modifier, we don't need a 28-day dermal tox and we don't need the mammalian genotox?

DR. EISENMANN: Correct.

DR. HILL: If it's only used in that use, then actually the ingredient itself is never making it into the system or onto the skin or anything. It's modifying the surface of something that is.

MR. GREMILLION: Sorry, could you explain the surface modifier. It's not actually an ingredient? How does that relate to the cosmetic products that --

DR. HILL: Page 47. I don't know if you have the PDF. It shows the chemistry.

DR. MARKS: Forty-seven.

MR. JOHNSON: It was 41 I thought.

DR. MARKS: Pardon?

MR. JOHNSON: It was on PDF 41.

DR. MARKS: Okay. I was going to say 47 gives me --

DR. HILL: Forty-one, I'm sorry.

DR. MARKS: -- testing. Oh, yeah. Excellent, not stable to acid.

DR. SHANK: In fact, it's not an ingredient in formulations. This is part of a method of manufacture of something. But this is not what we would call a cosmetic ingredient. Is that correct?

DR. EISENMANN: Yeah. It usually is identified as an ingredient. But it is a component of these modified pigments -- colors.

DR. HILL: It would be akin to the indirect uses in food, I think. But even there I'm not even sure that's accurate, because there's no residue of that ingredient itself. It no longer exists.

DR. SLAGA: It's just not penetrating.

MS. FIUME: Carol, could I just ask for clarification? I understand that the color -- but in products like cleansing and face products and moisturizing products, there's a pigmented fraction of those that this is

with, even like with cleansing products? It's not just necessarily to give --

DR. EISENMANN: Correct. That's my understanding. That's its only use.

MS. FIUME: Will we receive something, in writing, that tells us that that is the only use, so what we can have it documented?

DR. HILL: I think we put it in the report as this is what we're clearing for safety and we don't know if that's the only use.

DR. EISENMANN: And that's the only use -- right.

DR. KOWCZ: It's the only use for now.

DR. EISENMANN: That's what we would find acceptable for you to do.

DR. HILL: What I like about that is, if you read the de Graaf paper, you come to the conclusion that we don't really know very much about titanium sensitivity, except that it seems that patients that have titanium implants sometimes, somehow, end up cross sensitizing. And we're not sure why that is yet, if I read the de Graaf paper carefully. Because it might be the titanium, but maybe not.

The salicylate that's in here, that's reported as a preservative function. I know that there is extemporaneous compounding in the stuff going on out there for dermal application, but it seems to be off everybody's official map. That's not a good reason to keep it in here. I think we put these together and left them last time, administratively, so we could have some actual toxicology information, because most of that's going to come from the citrate.

And that's also true in the de Graaf paper; they have the citrate and the lactate -- and I forget what the others -- there are several others. But they had oxalate. Some of those results, I think are equiv -- because oxalic acid is irritating. And there's another one that's actually the oxalate that's named differently, but it's still the oxalate.

I don't know where I landed in all that big long babble, except to say I agree with what they're saying; because what it does is it kicks the can, keeping the use that is clearly being used. The only issue that's raised, from where I sit, is then do we have to look at the safety somewhere down the line of the actual ingredient that's the surface modified, whatever these are.

If we're not actually putting titanium -- what is it again? Isopropyl titanium triisostearate in the cosmetic product because it's reacted and it's on the surface of something else. Let's see, which one was it that we --

DR. MARKS: I guess I need to get, in my own mind, a better understanding of what -- again, what Ron Hill and what you brought up. What a surface modifier is. How does it work? And is it an ingredient or not an ingredient? We're obviously including it as an ingredient. I assume it's in the dictionary.

MR. JOHNSON: Yeah. That's the only function.

DR. MARKS: And the function can be handled. But does that negate needing the 28-day dermal tox and the mammalian genotox? Is this saying that it's not in contact with the skin? I don't quite understand.

DR. SLAGA: Well, if it's in contact, it's on the surface.

DR. HILL: But it no longer exists as that compound, that's the point.

DR. SLAGA: It's just not going to penetrate.

DR. MARKS: Okay.

DR. HILL: And according to this, it doesn't exist as that compound anymore. It's modified a pigment. Is it skin pigment? I assume it's not skin pigment. I assume they're talking about some other pigment in the formulation.

DR. MARKS: Can you answer that technical question? What's the pigment it modifies?

DR. EISENMANN: Well, the sample they gave was iron oxides.

DR. MARKS: Okay. So, it's pigment in the cosmetic formulation. I assume when you ask that question, Ron Hill, it's not the pigment in the skin, obviously; then it'd be absorbed if it were.

DR. HILL: In the case of the black iron oxide, what's actually happened is the iron oxide has reacted with the isopropyl titanium triisostearate, knocking off the isopropanol and now we have a covalent bound between the oxygen on the iron oxide and the titanium; so, iron oxygen titanium, and it's covalently bound there.

Now, I don't know how tight that iron oxygen bound is, but my guess is it isn't going anywhere from that pigment. If that's the use -- I'm trying to remember what the surface modifiers were that we made a cage around --

DR. EISENMANN: Polysilicones.

DR. HILL: That's it. The polysilicones. Where the only use was to modify the flow of the iron particles or whatever metal -- it was iron I think again. So, you had a color compound in there with different flow characteristics. And then the question is, should we be reviewing those particular iron oxide particles as an

ingredient, but that's not what we're called to do today, I don't guess.

DR. MARKS: Let's kind of finish up with the isopropyl titanium triisostearate. Carol made the suggestion that we could move forward and eliminate that ingredient from the insufficient data. And we could move forward, safe, because of its use only as a surface modifier. Is that a reasonable -- presumably -- non presumably -- we will be issuing a tentative report. I'll be seconding a conclusion, but I want to make sure we have our conclusion.

Do you like that idea of the isopropyl titanium triisostearate being safe when used as a surface modifier only? And I think we could either put that in the conclusion, we'll get to that. Or we could just say, when we say as use, then obviously in the discussion it'd have to be very clear that that's the only use that we're approving it for. Tom, Ron, Ron?

DR. SLAGA: If it's only used as a surface modifier, I agree.

DR. MARKS: Ron Shank, you're thinking. I can see that. You don't have to say you're thinking.

DR. SHANK: No. I'm looking at it the way people not familiar with this kind of thing. When you say it's a surface modifier, that's all you're going to say in the discussion.

DR. SLAGA: Or it could be more.

DR. SHANK: It has to be that it cannot penetrate the skin.

DR. MARKS: Right. I think we'd have to put in the discussion if it were, the data needs we want, the 28-day dermal tox and the mammalian genotox. And that's our concerns if this would be absorbed.

DR. SHANK: We'd need absorption first.

DR. MARKS: Yeah.

DR. HILL: Those would be no longer applicable.

DR. MARKS: Exactly.

DR. HILL: And then I think you'd have to present this modification chemistry right up in the front, in the chemistry section of the document, so everybody is clear that we no longer have isopropyl titanium triisostearate. But we have the triisostearyl titanium covalent linked through oxygen bridge to the iron. Or it wouldn't have to be iron oxide, but this is the one we know about.

DR. MARKS: Okay.

MR. JOHNSON: I just have a question. If that ingredient is going to be bound, how are the data on black iron oxide, with 2 percent isopropyl titanium triisostearate, being used to evaluate the safety of isopropyl titanium triisostearate?

DR. HILL: It's being used to evaluate it in that particular use. Because you no longer have isopropyl titanium triisostearate, you have exactly what's depicted in that slide.

MR. JOHNSON: The complex. Yeah. So, the complex is what you have?

DR. BERGFELD: Could I ask a question, Ron? The titanium is described in its physical characteristic as reddish. And when you put iron oxide to that -- and we can say that most of the products that are cosmetic products are in the whitish range of color or no color. How does that happen?

DR. HILL: The isopropyl titanium triisostearate, I'm puzzled when it says that's a reddish liquid because I doubt it. The question is what that actually is. And it gives Reference 4, which is Kenrich Petrochemicals. I wonder if it's a suspension of those iron particles that they're actually saying is a reddish liquid. I think we need to get clarification.

MR. GREMILLION: I've got a clarifying question on the use as a surface material. If I understand this isopropyl titanium triisostearate is not actually an ingredient, it's something used in the method of manufacturing that turns into another compound. And so, the concentration of use is zero for this compound, and another compound that has iron in it is actually the ingredient that should be evaluated. Is that a correct characterization?

MS. KOWCZ: I think that's a good question, but it's different topic. Because you have this -- the isopropyl is modifying the actual iron oxide. The iron oxide is a whole different topic. And I think, Ron, you said it from it from the very start, it's a different class.

DR. HILL: It probably shouldn't be an ingredient if that's the only use. The ingredient is actually what's sold to the formulators, would in fact be the surface modified iron particles. But then again, we already reviewed the silicones used in that way even thought that was the same case. I'm not sure how to think about that.

But I wondered about this from the get-go because again, we have information that tetraethoxy doesn't last very long in water. I thought well okay, but the stearyl moiety are shielding that reactivity. And it lasts a good bit longer if it's used itself.

We don't have information to know that it isn't used itself; but we can write it to say that we're clearing it for this use and nothing else, just like we do for use on nails. Just like we did with those silicones for coding the iron and be done with it.

Now, do you have adequate toxicology on the iron particles that are actually resulting? That's not what we're reviewing today.

DR. MARKS: Right.

MS. FIUME: Alex and Carol, then, when it's being used as a surface modifier, is it going to be named on the ingredient list for the cosmetic?

MS. KOWCZ: Yeah. It's identified. It's 2 percent of the actual ingredient, yes.

MS. FIUME: It's basically a trade-name mixture.

MS. KOWCZ: It's identified on the ingredient label, absolutely.

DR. EISENMANN: Right, the mixture.

DR. MARKS: I'm going to change subjects now. I think we've a little bit -- Ron Hill, you and Dan had a robust discussion, last meeting, which is on page 20 about the chemistry and which ingredients belong in the report. At that point, we settled with all the ones listed here, the four that are insufficient. Are you happy, at this point, moving forward with having five ingredients in this report? The ones named here? Because I don't know if that will come up tomorrow or not.

DR. HILL: I'm comfortable with leaving them.

DR. MARKS: Okay good.

DR. HILL: And having them be insufficient.

DR. MARKS: Okay.

DR. HILL: Because they won't get lost in the crowd that way. That's just me.

DR. MARKS: Okay. Let me see where we are with this, team. After a robust discussion about -- I'll call it ITT -- the isopropyl titanium triisostearate only being used as a surface modifier, that we could move forward with a tentative report, with a conclusion that isopropyl titanium triisostearate is safe as a surface modifier. And for the remaining four titanium, we have insufficient data. And that's listed in the memo.

DR. SLAGA: Very good.

DR. MARKS: Sound good? Ron, I see shaking okay. Wilbur, you have another question?

MR. JOHNSON: Yes. So, there's no need for 28-day dermal toxicity data on black iron oxide with 2 percent isopropyl titanium triisostearate, or genotoxicity data on that complex?

DR. HILL: Right.

DR. MARKS: Yes.

MR. JOHNSON: Okay.

DR. MARKS: It's basically, if it were to be used in any other -- and this could be in the discussion, I think we've talked about it. If the ITT had any other use, other than a surface modifier in the future, we would expect that a 28-day dermal tox and a mammalian genotox would be the data we would need. That's obviously going to be in the minutes from the last meeting.

This meeting, I don't know. Ron, Ron, and Tom what's your feeling about putting that in the discussion? Because everything hinges on going safe that this is a surface modifier use only. I think we could put that, so that if somebody's looking to change for another use for ITT, they would know what our thoughts were now was we need a 28-day dermal tox, and a mammalian genotoxicity, if you feel that it's safe for other uses. Did you catch that Wilbur?

MR. JOHNSON: Yes.

DR. MARKS: Then just put those needs in the discussion.

DR. HILL: Yeah. We would be in a particulate mode where presumably absorption wouldn't come into play. And then we should get a clarification in that case. Is this 1.5 percent in a leave-on -- you could find out who sent you that information. Is that calculated based on titanium?

In other words, it wouldn't be 1.5 percent weight titanium, but based on the molecular weight of that isopropyl titanium triisostearate. Or is that iron in all? It's probably somehow calculated back to the ingredient, but we should clarify. Because maybe it's not that high. It probably is.

DR. BERGFELD: Jim, before you go on, can you make comment to the article that was sent to us? *A Retrospective Study of Titanium Sensitivity: Patch Test.*

DR. MARKS: Yeah. Let me see if I have that here. I think I do. First of all, it was retrospective. And one of the points of the study was to see which titanium salt was the best at detecting allergic contact dermatitis, and they got different -- as based on positive patch test reactions. The different salts gave different reactions. Meaning percentage of reaction.

As I recollect, the author said there's no one titanium which will cover all of them. And to me that was the biggest takeaway. Let me see was there -- yeah, "…single titanium salt cannot be used as a patch test preparation because specific patient responses occur…." Boy. "Their accuracy in" -- and this is probably the most important. Not only that one that there's not one salt, but also that, "Their accuracy in diagnosing titanium sensitivity is unknown." And the real key is what relevance does this positive patch test have to a metal implant. And that's totally unknown.

I think the authors were trying to go back -- look at their past data with patch testing all these salts and seeing which is the best; and unfortunately, there was not one that came out in the lead. That's how I interpret.

DR. BERGFELD: So, did I.

DR. MARKS: I only patch test with one salt, but, you know, you do the best you can.

MR. JOHNSON: Should this study be added or not?

DR. BERGFELD: Yeah. Well, it is relevant to any patch testing in the human model.

DR. SLAGA: Yeah. It is relevant.

MR. JOHNSON: Because I know some of the titanium salts that are included in that study are not cosmetic ingredients.

DR. MARKS: Right.

MR. JOHNSON: For example, titanium dioxide is among those testing.

DR. MARKS: The answer would be, yes, I would add it as data, since it's relevant to sensitivity to titanium salts. But ultimately, how does it change -- I think if somebody thinks the titanium is not a sensitizer, then maybe this article would help convince you it could be in rare cases.

DR. EISENMANN: One of the reasons why I sent the paper over to them was because there's a statement in the discussion that says, the panel noted the likelihood that any toxic effects of these ingredients would primarily be due to the titanium component. And I don't know. If you believe that, then you need references on titanium, don't you?

I mean, I don't know if there was a search for titanium. Either that statement needs to go, or there should be a little bit more effort to look at the titanium. If the effects are going to be due to titanium, then there should be a little bit more effort to look for studies on titanium. And this paper might be helpful to say, oh, titanium dioxide's not relevant. But maybe some of the other titanium salts --

DR. MARKS: I think for the ingredient here we have -- particularly, the one that we're going to move forward with a safe conclusion -- we have a human sensitization study, that at the use concentration it's safe. I guess indirectly this article has some relevance. But we've already answered the question of sensitivity with the isopropyl titanium triisostearate.

DR. HILL: I don't concur with that statement where it says the panel -- I don't concur.

DR. EISENMANN: Well, I didn't either. I'd be fine with you taking that statement out.

DR. HILL: I don't concur. And I did have a question on that note, is that there was -- on page 26, there's an ADME study where they did something in vitro. And then it's in a Pakistani Journal article so I don't know if it's in English or there was translation error. But the units that were given in your write-up are not consistent with mass transfer or uptake, so that has to be checked and I flagged it.

But beyond that, we don't have solid systemic titanium data on which to hang our hat. We do know that the implant use has been approved, but that's titanium metal. I have one right in here. If you remember, I was snaggletooth for a couple meetings. We'll see what happens over the long term, but anyway, I feel confident.

DR. BERGFELD: Allergies.

DR. HILL: I feel confident right now, though; it's better than mercury being in there, in the filling. Anyway, but that's the other beauty of this surface modifier. And we do have to decide what's in the discussion, is that you're not liberating titanium; because now it's attached to the particle and it's not going anywhere.

And titanium oxide is well characterized. And so that's the thing. I looked at this tetraethoxide and I thought, you're going to end up with titanium oxide. And that might also be true of the stearates. It's clearly not true of the salicylate. We do have information that titanium salicylate ends up as titanium salicylate in the urine, so that's interesting.

You've got some information in there. but I don't know that we have any long-term data to suggest that anything cosmetically relevant is titanium-based safety concern -- toxic. I mean, I don't see anything.

MR. JOHNSON: Titanium citrate is the only ingredient that's being reviewed in this safety assessment, that was tested in that particular study.

DR. MARKS: Right.

MR. JOHNSON: Should we include just the data on titanium citrate, or data on titanium dioxide

and other salts in this summary?

DR. HILL: My personal opinion is you don't include the titanium dioxide, other than you could certainly make a mention -- which I think you already did -- of the general innocuousness, unless we're into particle concerns. I think that de Graaf paper did speak to using titanium dioxide for patch testing and seeing essentially no activity of note.

What about data from something like titanium chloride? Something that's soluble besides the citrate or -- citrate and lactate are the best in terms of delivering potentially absorbable titanium.

DR. MARKS: Wilbur, for Wave 2, you had written up a section. And I didn't have any problem with that. You summarized the conduct of the study, starting right off though as retrospective. You gave the results and then I thought the conclusions were well stated.

I don't have any problem adding that if somebody wants to go back and refer. I think ignoring it is not the best. Because, as you said, one of the ingredients that are in this is mentioned in that paper. I don't think it alters our conclusions at all, but I do think it adds more data if somebody wants to review the subject. And to me that's good. If the data were irrelevant, or in question, and we've had that discussion, but I don't think so in this case.

MR. JOHNSON: It's okay to include data on --

DR. MARKS: I think so. Other team member, did you read the Wave 2 that --

DR. SLAGA: I would include it.

MR. JOHNSON: But on the other salts, other than titanium citrate. Just let those remain in here?

DR. MARKS: Yeah. I'd leave them in, you mentioned that in there.

DR. HILL: I think it is also worth noting, though, that on the one that was done with titanium for isopropoxide, there was not a dose-dependent effect. I mean, pretty much it stayed the same across the board, which to me is noteworthy. That was one that jumped -- and I flagged that in the comments to Wave 2.

DR. MARKS: Really good discussion. Again, I'll reiterate, presumably, I'm going to be seconding a motion that a tentative report be issued with the titanium complexes. The conclusion will be the isopropyl titanium triisostearate is safe as used as a surface modifier, and insufficient data for the remaining four titanium. And that data needs are listed in Wilbur's memo. Sound good?

DR. SLAGA: Sounds good.

MS. FIUME: And can I just make sure, Wilbur, do you have enough information from the discussion to address the surface modifier use? Or is there more information that you need from the team?

MR. JOHNSON: Well, you know, basically, what the team has said is that if the ingredient has uses other than that of a surface modifier, then the 28-day dermal toxicity data, and the genotoxicity data, would be needed. But is there any more with respect to that issue that should be mentioned?

DR. MARKS: I don't think so.

MS. FIUME: Specifically, to the surface modifier aspect of it?

MR. JOHNSON: Yeah. Well, it's my understanding that you're talking about a complex, you're not dealing with free ingredients.

DR. MARKS: Yeah. And I would be sure to run that by Alex and Carol so that the actual -- to address the issue of what the surface modifier really is.

MR. GREMILLION: The 1.5 percent concentration, I really don't understand what that refers to.

DR. MARKS: Presumably, when it's formulated, that the percentage of -- the ITT is put into the formulation.

MS. KOWCZ: That you put into the product.

DR. EISENMANN: What I asked for is the concentration of the named ingredient. So, it should be the concentration of the isopropyl titanium triisostearate.

DR. HILL: But if it's modifying the surface, the reality is that concentration is zero, or somewhere near zero.

DR. EISENMANN: Understood.

DR. MARKS: But I think that's what needs to be captured in the discussion.

DR. HILL: And if they've calculated --

DR. MARKS: Once it's put together, then it becomes essentially zero from a biologic toxicologic point of view. And that's why we don't need the two data needs which we had identified previously, the 28-day tox and the --

MR. JOHNSON: Because it doesn't exist in formulation.

DR. MARKS: Correct. And I think that's what needs to be clarified so those of us, who are not

surface modifier chemists, understand that. And I think, Alex, you and Carol can help Wilbur do the wordsmithing to make that clear.

I kind of like the way you said it, Ron Hill. We put X percentage in the formula, and once it's formulated it becomes zero, in terms of essentially availability to the skin.

Okay, any other discussion points? Wilbur, you okay?

MR. JOHNSON: Yes. I am. Thank you.

DR. MARKS: Good. Okay. Thank you everyone. That was really good.

Day 2 of the September 24-25, 2018 CIR Expert Panel Meeting – Full Panel

Titanium Complexes

DR. BELSITO: At the June meeting we issued an insufficient data announcement. I won't go through it all because it came out at yesterday's meeting that these are apparently used as coatings rather than as independent ingredients. And we thought we should table this for clarification and rewriting of the document.

DR. BERGFELD: And that's a motion to table?

DR. BELSITO: Yes.

DR. BERGFELD: Is there a second?

DR. MARKS: We'll second that. We can give you the way we were going to move forward.

DR. BERGFELD: There's no discussion on table, so all those in favor of tabling? All right, thank you. Unanimous. Discussion now?

DR. MARKS: We also had a great deal of trying to figure out what a surface modifier was, Don, and your team. We were reassured with the isopropyl titanium triisostearate that that was safe, and an inclusion would be as a surface modifier. We didn't feel comfortable with the other four titaniums; so, we would project they would be in an insufficient conclusion unless we received more data.

DR. BERGFELD: Well, that'll be reflected in the minutes. Any other comments by the Belsito team?

DR. BELSITO: I just felt that this all came out at our meeting yesterday, and then there was a report that was circulated; it was to help us looking back at when we dealt with other surface modifiers. But the general public had not had a chance to comment on this; and therefore, it would be more appropriate to table it and have that information available to everyone for input.

DR. BERGFELD: Alex, do you want to make a comment regarding the PCP handling of this ingredient?

MS. KOWCZ: We were on the Dr. Marks team, and we do know that it's covalent bonded. We know that it's a surface modifier, the specific isostearate that we talked about. I don't know what other additional data, whether you want something about the surface modification. I'm not clear about what additional data would clear this material.

DR. BERGFELD: Okay.

DR. BELSITO: I'm asking for whatever data you have. I just think that when very new information comes out, at a meeting, where there aren't chances for other potentially interested parties to comment, then it should be tabled and brought forth, as we usually do, with 60 days announcements for individuals to respond if they have issues.

MS. KOWCZ: We're fine with that.

DR. HELDRETH: If I may interject on here.

DR. BERGFELD: Sure.

DR. HELDRETH: Typically, if we put out something that's tabled, it doesn't go out for a 60-day comment period. What goes out for a comment period, is if we put out a tentative report. So, we could put this out as a new tentative report, asking for that those changes to be put into the report. And then that would have a technically, official 60-day comment period for everybody to realize the changes for that one ingredient.

Also note, that for that one ingredient we have data suggesting that it's a surface modifier and has this covalent structure, but we do not have such data for any of the other ingredients in the report. As far as we can tell from the data, those other ingredients in the report are still small, discrete molecules.

DR. BERGFELD: A question that I have, the minutes do go out and are posted, are they not?

DR. HELDRETH: The post-meeting announcement will go out on Friday.

DR. BERGFELD: Right. And so, it will be in the minutes. And also, what would you be doing to advertise this particular issue on this tabled ingredient? Carol?

DR. EISENMANN: We also have a post-meeting announcement that gets sent out; and then we'll discuss it at the CIR SCC meeting. And, there's also another committee, the Scientific -- SRTC -- Regulatory Toxicology Committee; we'll discuss it at that meeting also.

DR. BERGFELD: So, it will be, in some way, disseminated to the public and interested parties.

DR. EISENMANN: I will contact the companies that provided the HRIPT, so I heard there was interest in knowing for sure whether or not -- what that material was. Because that came in before I knew it was a surface modifier only.

DR. BELSITO: Okay -- go ahead.

DR. BERGFELD: Go ahead, Ron Hill.

DR. HILL: I was just going to say we did ask for clarification of what the meaning of the concentration of use was in the context of that application as well; so hopefully, that can be discussed and clarified.

DR. GREMILLION: Right now, it says one and a half percent for this ingredient; but what I'm understanding is when it's used in the product, it forms a bond and becomes another substance. And so, is some of that one and a half percent persisting? Or, you know, is that used as a justification to not do the normal analysis on that ingredient? And I think that could be clearer.

DR. BERGFELD: Any other discussion?

MR. JOHNSON: I'd just like for it to be reiterated exactly what the panel needs from industry.

DR. BERGFELD: Don?

DR. BELSITO: At this point, what we're saying was that we wanted it clarified that isopropyl titanium triisostearate is used only as a surface modifier, and not used for other purposes. That the other titanium salts are not used as surface modifiers, or what they are used at. And I think there's a good question that was raised, after modification of whatever the surfaces they're modifying, is there residual left? Or is this something that is added to a bead, and then the beads come off, and then the beads are added to the final product?

MS. KOWCZ: We will definitely get that information for the next meeting.

DR. BERGFELD: Linda, any comment?

MS. KATZ: No.

DR. BERGFELD: Bart?

DR. HELDRETH: By all means it's the prerogative of the panel if they want to table it; that's absolutely your choice. However, I would ask if you're going to proceed with the table, to set up some sort of a timeline for when this comes back. Because when you table something, it may just kind of drift off under the ether unless we set a schedule.

DR. BELSITO: Then I'm okay with saying that it's insufficient for the citrate, the ethoxide, the titanium isostearate, and the titanium salicylate for everything that we asked for before, with the exception of we now have dermal irritation and sensitization on titanium citrate. That was given to us in Wave 2, so we don't need that information anymore.

And that the isopropyl titanium triisostearate appears to be safe as used for a surface modifier, but we would like clarification on residual material in those -- whatever surfaces they use to modify.

DR. BERGFELD: Are you requesting that for the December meeting or the March meeting?

DR. BELSITO: I think it depends upon whenever CIR wants --

DR. BERGFELD: Well, within the year? Bart's asking you for a timeline on it.

DR. BELSITO: No, he was asking for a timeline on the table.

DR. BERGFELD: Yes, just so I'm asking do you want to hear back --

DR. BELSITO: I'm saying I'm fine not tabling it.

DR. BERGFELD: Oh, so you're going to rescind your table? Okay.

DR. BELSITO: Let's proceed with an insufficient data announcement. Including insufficient for the isopropyl trisodium triisostearate, to determine exactly is there any residual, unreactive material after this coating that goes into formulation.

DR. BERGFELD: I understand. So, you're rescinding your table? You made the motion to table. Will you rescind your table?

DR. BELSITO: Yes.

DR. BERGFELD: Second?

DR. MARKS: Yes. But I would, rather than doing a second insufficient data announcement, I would move it for the tentative report. Then there would be a timeline on it. And just what you said reiterating, Don, the conclusion for the isopropyl titanium triisostearate; we said the conclusion would be safe as a surface modifier. And we would ask how much residual, but we think it would be very little based on what we've heard, and the low concentration used to begin with. So, we feel we could move on with a tentative report.

DR. BELSITO: Fine.

DR. BERGFELD: Well, we have rescinded the table. Now we have a proposal to go a tentative insufficient?

DR. MARKS: No.

DR. BELSITO: No.

DR. MARKS: Not tentative insufficient, a split conclusion.

DR. BERGFELD: Split conclusion.

DR. MARKS: Safe for isopropyl titanium triisostearate, when used as a surface modifier.

Insufficient for the remaining four titaniums. And Don elucidated those; for most of them we need all the information that was on the memo.

DR. BELSITO: Same as what we asked for before, except for dermal sensitization and irritation for the citrate.

DR. BERGFELD: So, I'm assuming we have a motion and a second. Is that correct?

DR. BELSITO: Yes.

DR. GREMILLION: Can I ask --

DR. BERGFELD: Yes, please.

DR. GREMILLION: So, the safety of use as a surface modifier doesn't depend on how much residual is left over.

DR. BELSITO: We're asking for that and we could always change our conclusion.

DR. MARKS: Yes.

DR. HELDRETH: And so, the pathway that this will take, since there are substantive changes to the conclusion, is this will come back as an amended tentative assessment. So, there will actually still be two more opportunities for --

DR. MARKS: Maybe. I mean, if we like this conclusion it'll go on to the final, next time, because we've already done the insufficient data announcement. We're purposing this as a tentative report. And the next time we see it we may want to amend it, or we may want to go on to final.

DR. BERGFELD: Is everyone in concurrence with that -- Ron Hill?

DR. HILL: It's fine. I just wanted to point out that tabling it, in this case until December, would have had the same effect because there's not time for the 90-day comment period between now and the December meeting. So, we're dealing with this in March, or we're dealing with this in March.

DR. BELSITO: It's 60-day comment period.

DR. HILL: Oh, is it 60? But, there's not 60 days, or there just barely is between now and December? Okay, all right.

DR. BERGFELD: All right. Well, we have a motion that's been restated, and it's been seconded, and we had a lot of discussion. May I call to question now? All those in favor of the conclusion? Thank you. Unanimous.

MR. JOHNSON: Just one comment.

DR. BERGFELD: Yes, Wilbur, please.

MR. JOHNSON: So, Dr. Belsito, the needs that you mentioned relating to the chemistry of that ingredient, should be stated in the discussion section clarifying --

DR. MARKS: The needs are on the four titaniums. The ITT, we don't have a need at this point, but the discussion really needs to elucidate what a surface modifier is.

DR. BELSITO: And whether there're any residual amounts of isopropyl titanium triisostearate in whatever this is coated on.

DR. LIEBLER: That applies to all of the ingredients.

DR. MARKS: Yes.

MR. JOHNSON: Okay. And so those needs should be stated in the discussion section.

DR. BELSITO: Yes.

MR. JOHNSON: Okay.

DR. BERGFELD: Anything else?

MR. JOHNSON: That's all I have.

DR. BERGFELD: Does everyone understand what's been done here? We've had a lot of comment, but hopefully -- Wilbur says he has what he needs. So, we'll move on then to the next ingredient, which is the Vinylpyrrolidone Polymers, Dr. Marks.

Safety Assessment of Titanium Complexes as Used in Cosmetics

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The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, 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 C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of 5 titanium complexes in cosmetic products; these ingredients have the following reported functions in cosmetics: Isopropyl Titanium Triisostearate (surface modifiers), Titanium Citrate (colorants; humectants), Titanium Ethoxide (binders), Titanium Isostearates (film formers; opacifying agents), and Titanium Salicylate (preservatives). The Panel reviewed relevant data relating to the safety of these ingredients in cosmetic formulations and issued the following separate conclusions: Isopropyl Titanium Triisostearate is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when used as a surface modifier. The data are insufficient to determine the safety of Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, and Titanium Salicylate.

INTRODUCTION

The safety of the following 5 titanium complexes, as used in cosmetics, is reviewed in this CIR safety assessment.

Isopropyl Titanium Triisostearate	Titanium Ethoxide	Titanium Salicylate
Titanium Citrate	Titanium Isostearates	

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), the titanium complexes are reported to have the following functions in cosmetics: Isopropyl Titanium Triisostearate, surface modifier; Titanium Citrate, colorant and humectant; Titanium Ethoxide, binder; Titanium Isostearates, film former and opacifying agent; and Titanium Salicylate, preservative (Table 1).[1] These ingredients are all tetravalent complexes of titanium, with a high degree of covalent character in the bonds between oxygen and titanium. However, Isopropyl Titanium Triisostearate appears to be unique, as it is utilized to react with colorant particles, forming a modified surface on those particles.

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

CHEMISTRY

Definition and General Characterization

The definitions, structures, and functions in cosmetics of these ingredients are presented in Table 1.[1] The ingredients in this group are tetravalent complexes of titanium.

$$Ti^{n+}\left[R^{m-}\right]_x$$

Figure 1. Generic formula of titanium complexes.

When the oxidation state of titanium is 4+ or greater ("n+" > 4 in Figure 1) the titanium-bonding character is coordinate. The ingredients in this report are presumed to all comprise complexes of titanium wherein the oxidation state is 4+. Accordingly, structures for these chemicals have been drawn with coordinate oxygen-titanium bonds for the sake of convenience (Figure 2).

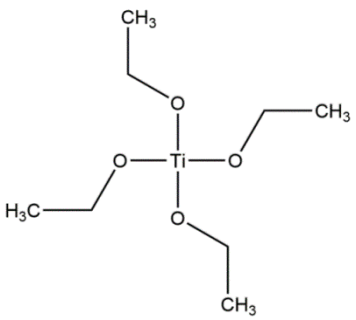


Figure 2. Titanium Ethoxide

However, according to information received from a manufacturer, Isopropyl Titanium Triisostearate is not supplied as a discrete chemical, but is used in cosmetics as a surface modifier. Specifically, this ingredient is reacted with pigment particles (e.g., black iron oxide) to create a coating, and is supplied for formulation as such coated particles (Figure 3). Thus, the presence of any residual or unreacted Isopropyl Titanium Triisostearate in the product formulation would be considered an impurity.

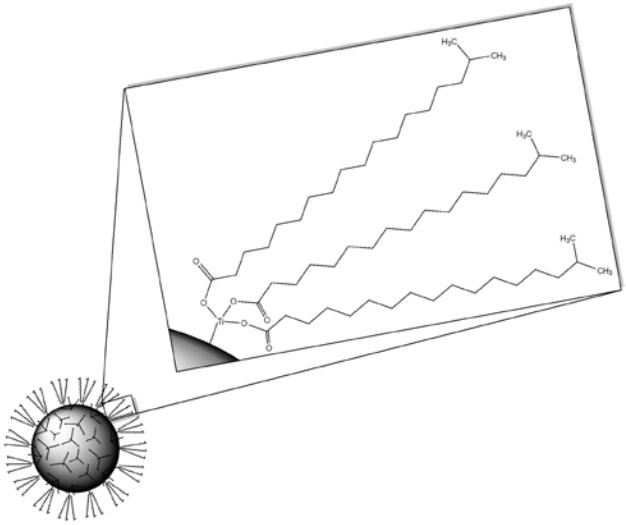


Figure 3. Idealized view of a pigment particle, surface modified by reaction with Isopropyl Titanium Triisostearate (depicted isostearyl chains are one example of an "iso")

No data have been submitted to suggest that Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, or Titanium Salicylate are used in cosmetic formulations to modify pigment surfaces in this way. Accordingly, the available information suggests that these four ingredients are discrete, unreacted complexes (e.g., Figure 2).

Chemical and Physical Properties

Titanium Citrate and Titanium Ethoxide are soluble in water, whereas Isopropyl Titanium Triisostearate is insoluble in water.[2,3,4] Notably, however, Titanium Ethoxide is rapidly hydrolyzed in water, with a reported half-life of as short as 3 to 5 minutes. The formula weights of Isopropyl Titanium Triisostearate, Titanium Ethoxide, and Titanium Salicylate are 961.4, 228.11, and 320.08, respectively. Properties of these ingredients are presented in Table 2. However, at least in some uses Isopropyl Titanium Triisostearate is reacted onto a hydrophilic pigment surface ((substrate) rendering the resulting surface hydrophobic) prior to formulation, resulting in a product of significantly higher formula weight.[5]

Method of Manufacture

Isopropyl Titanium Triisostearate

According to one supplier, Isopropyl Titanium Triisostearate is produced by reacting tetra-isopropyl titanate with 3 equivalents of isostearic acid.[4] The product is predominantly isopropyl tris(isostearoyl) titanate. However, it will also contain the tetra-isostearoyl titanate and the di-isopropyl di-isostearoyl titanate as well, as confirmed by nuclear resonance magnetic (NMR) spectroscopy and Fourier transform infrared (FTIR) analysis. There is no indication in this procedure that product is reacted with a colorant particle.

According to another supplier, Isopropyl Titanium Triisostearate is produced by reacting isopropyl tris(isostearoyl) titanate with a colorant particle (e.g., black iron oxide).[5] The result is the loss of isopropanol and the formation of a covalent bond between the titanium atom of tris(isostearoyl) titanate and an oxygen atom of the colorant particle. Thus, the surfaces of such particles are covalently modified such as in Figure 3.

Titanium Citrate

Titanium Citrate has been prepared by mixing titanium (III) chloride with a 1.2-fold excess of sodium citrate at a pH of 3.[6] Exposure to air resulted in the quantitative oxidation of titanium (III) citrate to colorless titanium (IV) citrate.

Composition & Impurities

Isopropyl Titanium Triisostearate

A chemical supplier has reported that an Isopropyl Titanium Triisostearate trade name material consists of 98% Isopropyl Titanium Triisostearate and < 2% isopropyl alcohol.[4]

The results of an impurities analysis of tetraisopropyl titanate (a titanium compound used in the manufacture of Isopropyl Titanium Triisostearate) indicated the presence of calcium (3 ppm) and titanium (16.99%).[7] Other metals were not detected. Polychlorinated biphenyls and the halogens, fluorine, chlorine, bromine, and iodine were also undetectable.

USE

Cosmetic

The safety of the titanium complexes is evaluated based on data received from the United States (US) Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics.[8] Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[9]

Only one of these titanium complexes is reported to be in use. According to 2019 VCRP data, Isopropyl Titanium Triisostearate is reported as being used in 513 cosmetic products (506 leave-on and 7 rinse-off products); half of the reported uses are in lipstick formulations (253).[8] The results of a concentration of use survey conducted by the Council in 2017 indicate that Isopropyl Titanium Triisostearate is used at concentrations up to 1.4 % in leave-on products (eye shadows) and at concentrations up to 0.3% in rinse-off products (eye make-up removers).[9] Further use frequency and concentration of use data are presented in Table 3. All reported use concentrations of Isopropyl Titanium Triisostearate in cosmetics relate to the use of this ingredient as a surface modifier.

According to the *Dictionary*, Titanium Citrate is reported to function as a colorant in cosmetics.[1] It should be noted that this ingredient does not appear on the list of color additives that are permitted for use in cosmetics in the US.[10]

Cosmetic products containing Isopropyl Titanium Triisostearate may be applied to the skin or, incidentally, may come in contact with the eyes (at maximum use concentrations up to 1.4% in eye shadows); this ingredient is applied to mucous membranes, and could be incidentally ingested (at maximum use concentrations up to 0.42% in lipstick). Products containing Isopropyl Titanium Triisostearate may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

Isopropyl Titanium Triisostearate is being used in face powders at concentrations ranging from 0.25% to 0.75%. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[11,12,13]

Non-Cosmetic

Titanium dioxide (which is not being reviewed in this safety assessment) is widely used in the preparation of anti-reflective coatings, and these titanium dioxide layers can be prepared by spin-coating a Titanium Ethoxide solution.[14] Titanium Ethoxide has also been used as a catalyst in the synthesis of *N*-acyl-*O*-ethyl-*N*,*O*-acetals.[15]

TOXICOKINETIC STUDIES

Dermal Penetration

Data on the dermal penetration of titanium complexes reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

Absorption, Distribution, Metabolism, and Excretion

In Vitro

Titanium Citrate

In an in vitro study using the rat (male Wistar rats) everted gut sac model, absorption (intestinal uptake) of titanium (from Titanium Citrate solution) was found to be a concentration-dependent process.[6] Titanium (IV) uptake through the intestine was approximately 200 to 300 µg/dl. The time frame of the study was not stated.

Human

Oral

Titanium Salicylate

Following the oral administration of titanium salicylates (~ 10 mg) to one human subject, titanium was detected in the feces and urine, with evidence that salicylate remained attached to titanium in the urine.[16] Details relating to the test protocol were not included. Though the definition of titanium salicylates is not provided in this study, it is possible that these data may be useful in evaluating Titanium Salicylate; therefore, when available, data on titanium salicylates are summarized throughout this report.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Isopropyl Titanium Triisostearate

The dermal toxicity of an Isopropyl Titanium Triisostearate trade name material was evaluated using New Zealand White rabbits (number of animals not stated).[17] It is not clear that Isopropyl Titanium Triisostearate was used as a surface modifier in this study. The test material was administered under a semi-occlusive wrap for 4 h. There were no signs of gross toxicity or remarkable pathology.

Oral

Isopropyl Titanium Triisostearate

The acute oral toxicity of an Isopropyl Titanium Triisostearate trade name material was evaluated using male and female Sprague-Dawley rats (number of animals not stated).[17] It is not clear that Isopropyl Titanium Triisostearate was used as a surface modifier in this study. An LD_{50} of > 30,000 mg/kg was reported for males only, females only, and males and females together. There were no signs of gross toxicity or remarkable pathology.

Ten barrier-reared albino rats of the Wistar strain (5 males, 5 females) were dosed orally with a suspension of black iron oxide with 2% Isopropyl Titanium Triisostearate (25% gravimetric corn oil suspension; effective concentration of Isopropyl Titanium Triisostearate = 0.5%).[18] Isopropyl Titanium Triisostearate was used as a surface modifier in this study. A single oral dose (5000 mg/kg) of the suspension was administered via gavage. Dosing was followed by a 14-day observation period, after which the animals were killed for gross necropsy. None of the animals died and there was no evidence of gross changes during the 14-day observation period.

Titanium Ethoxide

The acute oral toxicity of Titanium Ethoxide was evaluated at a dose of 2000 mg/kg body weight using 6 fasted female Wistar rats.[3] Dosing was followed by a 14-day observation period. Surviving animals were necropsied. None of the animals died. The mean body weight gain of animals was considered similar to that expected for non-treated animals of the same age and strain. There was no evidence of abnormalities at macroscopic post-mortem examination. The LD_{50} was > 2000 mg/kg body weight.

Parenteral

Titanium Salicylate

The injection of titanium salicylates (in water) "into the skin" of mice and rabbits (animal numbers and strains not stated) did not cause adverse effects.[16] However, tiny bumps were observed at injection sites and eventually disappeared. The doses administered and other details relating to the test protocol were not included.

Short-Term Toxicity Studies

Oral

Titanium Salicylate

The daily oral administration of titanium salicylates (10 g) "in bread given to rabbits" did not cause any adverse effects.[16] Details relating to the test protocol were not included.

Subchronic Toxicity Studies

Data on the subchronic toxicity of titanium complexes reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

Chronic Toxicity Studies

Data on the chronic toxicity of titanium complexes reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

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

GENOTOXICITY STUDIES

In Vitro

Isopropyl Titanium Triisostearate

The genotoxicity of an Isopropyl Titanium Triisostearate trade name material (98% Isopropyl Titanium Triisostearate and < 2% isopropyl alcohol) was studied using the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, TA1537, and TA1538.[17] It is not clear that Isopropyl Titanium Triisostearate was used as a surface modifier in this study. The trade name material was tested at doses ranging from 0.2 µg to 500 µg per plate with and without metabolic activation. No increase in the number of revertants per plate was observed with or without metabolic activation.

CARCINOGENICITY STUDIES

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

ANTI-TUMORIGENICITY STUDY

Titanium Citrate

The anti-tumorigenicity of Titanium Citrate in rats was evaluated using 2 groups of 46 rats with Jensen sarcoma.[16,19] One group was injected intramuscularly (i.m.) with Titanium Citrate (1 ml of 1 ppt titanium) in water, and the other group (control) was injected i.m. with ferrous citrate (1 ml of 1 ppt Fe). Long-term survivals were 88% for the group injected with Titanium Citrate and 39% for the group injected with ferrous citrate. Following 3 weeks of injections, the death rate in the control group was 5.5 times greater than in the test group, with 12% of the animals injected with Titanium Citrate dying and 61% of the control group dying from their tumors.

OTHER RELEVANT STUDIES

Cytotoxicity

Titanium Citrate

The structural effects of Titanium Citrate on the human erythrocyte membrane were studied in vitro using intact erythrocytes.[20] Erythrocytes were incubated with 0.1. 0.5, or 0.8 mM Titanium Citrate for 1 h and then examined using scanning electron microscopy (SEM). Erythrocyte deformations (both echinocytic and stomatocytic types) were observed at the concentrations tested. At a concentration of 0.1 mM, slight deformation (both types) was observed in a few erythrocytes. Titanium Citrate (0.5 mM) caused both types of deformation (mostly echinocytic) in the majority of the cell population. At a concentration of 0.8 mM, some stomatocytes and a few remaining echinocytes were observed, due to the intense hemolysis that affected the great majority of the erythrocytes. Numerous erythrocytes were ruptured, resulting in empty and retracted membranes (i.e., erythrocyte ghosts).

In another study, the effect of Titanium Citrate on human erythrocytes in vitro (1-h incubation period) was studied using SEM.[21] For a few of the erythrocytes incubated with 0.001 mM and 0.0005 mM Titanium Citrate, the shape appeared slightly deformed when compared to controls; the cellular diameter of treated cells was described as almost normal. At a concentration of 0.0025 mM titanium citrate, most of the erythrocytes had morphological alterations. Incubation with Titanium Citrate (0.005 mM) caused damage to erythrocytes, and the cells appeared smaller and more distorted. The morphological differences between treated and control erythrocytes were statistically significant.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The skin irritation and sensitization studies summarized below are presented in detail in Table 4.

Irritation

The skin irritation potential of an Isopropyl Titanium Triisostearate trade name material (98% Isopropyl Titanium Triisostearate and < 2% isopropyl alcohol) was evaluated using New Zealand White rabbits (number not stated).[17] It is not clear that Isopropyl Titanium Triisostearate was used as a surface modifier in this study. The undiluted test material was administered under a semi-occlusive wrap for 4 h. The test material was not corrosive. Black iron oxide with 2% Isopropyl Titanium Triisostearate was evaluated for skin irritation potential using 6 New Zealand white rabbits.[22] The test was applied under a 5 cm^2 occlusive patch for 24 h to intact and abraded test sites. The test substance did not cause skin irritation (primary irritation index (PII) = 0) at abraded or intact skin sites. The topical application of titanium salicylates (test concentration not stated) to the skin of rabbits (number and strain not stated) did not cause skin irritation.[16] The test concentration and other details relating to the test protocol were not included.

The skin irritation potential of a concealer containing 0.4% Isopropyl Titanium Triisostearate (undiluted; Isopropyl Titanium Triisostearate used as a surface modifier) was evaluated in a 24 h single insult occlusive patch test (SIOPT) involving 23 subjects.[23] Skin irritation was not observed in any of the subjects tested.

Sensitization

A human repeated insult patch test (HRIPT) on an eye powder containing 1.4% Isopropyl Titanium Triisostearate was performed using 101 subjects.[24] The test substance was non-irritating and non-sensitizing. Isopropyl Titanium Triisostearate did not function as a surface modifier in this eye powder. In another HRIPT (108 subjects), a foundation containing 0.433% Isopropyl Titanium Triisostearate (used as a surface modifier) was classified as a non-sensitizer.[25] The skin sensitization potential of a foundation containing 0.4% Isopropyl Titanium Triisostearate (used as a surface modifier) was evaluated in a maximization test involving 26 healthy subjects (24 females and 2 males).[26] No adverse or unexpected reactions were observed in any of the subjects during the induction phase. There was no evidence of contact allergy in any of the subjects after challenge patch application. Similarly, neither skin irritation nor sensitization was observed in an HRIPT (108 subjects) on a foundation containing 0.348% Isopropyl Titanium Triisostearate (used as a surface modifier).[27] HRIPTs on 3 leave-on products containing 0.276%, 0.281%, and 0.337% Isopropyl Titanium Triisostearate (used as a surface modifier) were performed using groups of 50 subjects (1 group per product tested). None of the 3 products induced allergic contact sensitization.[28] A foundation topcoat containing 0.102% Isopropyl Titanium Triisostearate (used as a surface modifier) was evaluated for its sensitization potential in an HRIPT involving 101 subjects.[29] There was no evidence of sensitization to the product.

Photosensitization/Phototoxicity

The phototoxicity of a pressed powder containing 0.004% Isopropyl Titanium Triisostearate was evaluated using 11 subjects.[30] The light source was a Xenon arc Solar Simulator (150W) with a continuous spectrum in the ultraviolet light, long wavelength (UVA; 320 to 400 nm) to mid-wavelength (UVB; 290 to 320 nm). A UVB absorbing filter that eliminated erythemogenic wavelengths (below 320 nm) was used for UVA dosing, but was removed for UVA/UVB dosing. The product (0.5 g) was applied for 24 h, under a 2 cm x 2 cm occlusive patch, to 2 separate sites (irradiated and non-irradiated). At approximately 24 h post-application (patch removal), 1 set of sites was irradiated with 24 J/cm^2 of UVA using a filtered light source; irradiation was followed by ½ minimal erythemal dose (MED) of UVB. The other set of sites served as a non-irradiated control. An additional area was irradiated (irradiated control) with 24 J/cm^2 of UVA, followed by ½ MED of UVB. All sites were evaluated after patch removal and 24 h and 48 h post-irradiation. There was no evidence of phototoxicity induced by the pressed powder containing 0.004% Isopropyl Titanium Triisostearate.

OCULAR IRRITATION STUDIES

In Vitro

Isopropyl Titanium Triisostearate

The ocular irritation potential of 2 foundation topcoats containing 0.102% Isopropyl Titanium Triisostearate (used as a surface modifier) was evaluated using the EpiOcular™ human cell construct (reconstructed human cornea-like epithelium).[31] Toxicity was measured by the reduction of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) to a blue formazan precipitate. The duration of exposure that resulted in a 50% decrease in MTT conversion in treated human cell constructs relative to control cultures (t_{50}) was determined (t_{50} > 24 h = non-irritating). Each foundation topcoat was tested alone and as a 50:50 mixture of the two. Human cell constructs were exposed to the test materials for up to 24 h. When the 2 foundation topcoats were tested alone, t_{50} values of 15.4 h and > 24 h were reported. The 50:50 mixture yielded a t_{50} of 15.2 h. The positive control (0.3% Triton®-X-100) yielded a t_{50} of 23.4 minutes. A conclusion describing the ocular irritation potential of the foundation topcoats was not stated. However, a t_{50} of < 24 h would be indicative of some degree of ocular irritation.

Animal

Isopropyl Titanium Triisostearate

The ocular irritation potential of an Isopropyl Titanium Triisostearate trade name material (98% Isopropyl Titanium Triisostearate and < 2% isopropyl alcohol) was evaluated using New Zealand White rabbits (number of animals not stated).[17] It is not clear that Isopropyl Titanium Triisostearate was used as a surface modifier in this study. The test material (0.1 ml) was instilled into the conjunctival sac, and scores for corneal opacity, iritis, and conjunctivitis were recorded at 1 h, 24 h, 48 h, and 72 h post-instillation. The following primary ocular irritation scores were reported: 10 (at 1 h), 0.7 (at 24 h), 0 (at 48 h), and 0 (at 72 h). There were no signs of gross toxicity or remarkable pathology. The test material was not corrosive.

An ocular irritation study on black iron oxide with 2% Isopropyl Titanium Triisostearate was performed using 6 New Zealand White rabbits.[18] Each animal received a single “intraocular” application (0.1 g) of the test substance. The eyes remained unrinsed for 24 h after instillation. Untreated contralateral eyes served as controls. Reactions were scored according to the Draize scale at 24 h, 48 h, and 72 h post-instillation. If any of the test substance remained in the eye at 24 h, the eye was rinsed with water after the 24-h reading. The test substance was classified as a minimal ocular irritant.

OTHER CLINICAL REPORTS

Retrospective Study

Titanium Citrate

A retrospective chart review was conducted on 458 patients who underwent patch testing with Titanium Citrate and other titanium salts, over a 10-year period.[32] The patch testing of titanium salts was performed at a dermatology clinic in the Netherlands, using Van der Bend chambers that were applied to the back for 48 h. Reactions were scored on days 2, 3, and 7 according to International Contact Dermatitis Research Group (ICDRG)/European Society of Contact Dermatitis (ESCD) criteria. Reactions identified as +, ++, or +++ were classified as positive, whereas doubtful reactions (?+) were not. At least one positive reaction was observed in 26 (5.7%) of the 458 patients patch tested. Fifteen (57.7%) of these 26 patients had a proven titanium-containing implant or reconstructive material. Also, most of the titanium-positive patients had local

symptoms, i.e., pain, erythema, dermatitis, pruritus, impaired wound healing, and swelling. For 16 (61.5%) of the 26 positive patients, complete or partial relevance of the positive result was determined. Overall, the percentage of positive reactions induced by each titanium salt was reported as follows: titanium (IV) oxalate hydrate (7.9%; 17 of 216 patients tested), titanium lactate (4.4%; 2 of 45 patients tested), titanium (IV) isopropoxide (2.9%; 8 of 272 patients tested), Titanium Citrate (2.2%; 1 of 45 patients tested), and titanium dioxide (0.9%; 3 of 329 patients tested).

Additional results presented relate to the fact that the 458 patients were divided into the following 3 groups: Group 1 (248 patients suspected of having titanium allergy), Group 2 (163 patients suspected of having metal allergy other than to titanium), and Group 3 (control group of 47 patients who were not exposed to titanium-containing medical devices and did not have a specific history of titanium allergy). The results (% positive reactions) are presented below:

Group 1: titanium (IV) isopropoxide (0.01%: 0.44% positive, 1 of 224 patients tested; 1% concentration: 1.78% positive, 4 of 224 patients tested; 5% concentration: 0.46% positive, 1 of 224 patients tested; and 10% concentration: 0.44% positive, 2 of 224 patients tested); Titanium Citrate (0.16% concentration: 2.70% positive, 1 of 37 patients tested; and 0.32% concentration: 2.70% positive, 1 of 37 patients tested [it is not stated whether the same patient reacted to both concentrations]); titanium lactate (0.16% concentration: 5.41% positive, 2 of 37 patients tested); and titanium dioxide (as is: 0.72% positive, 1 of 139 patients tested);

Group 2: titanium (IV) oxalate hydrate (5% concentration: 0% positive, 0 of 4 patients tested), titanium (IV) isopropoxide (up to 20% concentration: 0% positive, 0 of 4 patients tested); and titanium dioxide (as is: 1.26% positive, 2 of 159 patients tested);

Group 3: titanium (IV) oxalate hydrate (5% concentration: 5.26% positive, 2 of 38 patients tested), titanium (IV) isopropoxide (up to 20% concentration: 0% positive, 0 of 44 patients tested); Titanium Citrate (up to 0.32% concentration: 0% positive, 0 of 8 patients tested); titanium lactate (up to 0.24% concentration: 0% positive, 0 of 8 patients tested); and titanium dioxide (as is: 0% positive, 0 of 31 patients tested).[32]

SUMMARY

The safety of 5 titanium complexes as used in cosmetics is reviewed in this CIR safety assessment. According to the *Dictionary*, these titanium complexes are reported to have the following functions in cosmetics: Isopropyl Titanium Triisostearate, surface modifier; Titanium Citrate, colorant and humectant; Titanium Ethoxide, binder; Titanium Isostearates, film former and opacifying agent; and Titanium Salicylate, preservative. Isopropyl Titanium Triisostearate was tested as a surface modifier in the safety test data evaluated in this report, unless otherwise indicated.

According to 2019 VCRP data, Isopropyl Titanium Triisostearate is reported to be used in 513 cosmetic products (506 leave-on and 7 rinse-off products) ; half of the reported uses are in lipstick formulations (253). The results of a concentration of use survey conducted in 2017 indicate that Isopropyl Titanium Triisostearate is used at concentrations up to 1.4% in leave-on products (eye shadows) and at concentrations up to 0.3% in rinse-off products (eye make-up removers). All reported use concentrations of Isopropyl Titanium Triisostearate in cosmetics relate to the use of this ingredient as a surface modifier.

Titanium Citrate has been prepared by mixing titanium (III) chloride with sodium citrate, followed by exposure to air, which resulted in the quantitative oxidation of titanium (III) citrate to colorless titanium (IV) citrate. An Isopropyl Titanium Triisostearate trade name material is produced by reacting tetra-isopropyl titanate with 3 equivalents of isostearic acid. Methods of manufacture for the remaining titanium complexes in this safety assessment were not found. Whether or not this trade name material is being used as a surface modifier was not stated. The results of an impurities analysis of a titanium compound used in the manufacture of Isopropyl Titanium Triisostearate indicated the presence of calcium (0.0003%) and titanium (16.99%).

Following the oral administration of titanium salicylates (~ 10 mg) to one human subject, titanium was detected in the feces and urine, with evidence that salicylate remained attached to titanium in the urine. Though the definition of titanium salicylates is not provided in this study, it is possible that these data may be useful in evaluating the toxicokinetics of Titanium Salicylate.

There were no signs of gross toxicity or remarkable pathology in New Zealand White rabbits (number not stated), after application of an undiluted Isopropyl Titanium Triisostearate trade name material under a semi-occlusive wrap for 4 h. Whether or not this trade name material is being used as a surface modifier was not stated.

An acute oral LD_{50} of > 30,000 mg/kg was reported for male and female Sprague-Dawley rats (number not stated) dosed with an Isopropyl Titanium Triisostearate trade name material. Whether or not this trade name material is being used as a surface modifier was not stated. There were no signs of gross toxicity or remarkable pathology. In another oral toxicity study, 10 barrier-reared albino rats of the Wistar strain (5 males, 5 females) were dosed orally (5 g/kg) with a suspension of black iron oxide with 2% Isopropyl Titanium Triisostearate (25% gravimetric corn oil suspension; effective concentration of Isopropyl Titanium Triisostearate = 0.5%). None of the animals died and there was no evidence of gross changes during the 14-day observation period. In an acute oral toxicity study of Titanium Ethoxide involving female Wistar rats, the LD_{50} was > 2000 mg/kg body weight, and there was no evidence of abnormalities at macroscopic postmortem examination. The injection of titanium salicylates, in water, into mice and rabbits (animal numbers and strains not stated) did not cause adverse effects.

The short-term oral administration of titanium salicylates (10 g) in bread fed to rabbits did not cause any adverse effects. Subchronic, chronic, and developmental and reproductive toxicity studies on the titanium complexes reviewed in this safety assessment were neither found in the published literature, nor were unpublished studies submitted.

An Isopropyl Titanium Triisostearate trade name material was not genotoxic to the following *Salmonella typhimurium* strains when tested at doses up to 500 µg per plate with and without metabolic activation: TA98, TA100, TA1535, TA1537, and TA1538. Whether or not this trade name material is being used as a surface modifier was not stated. No published literature was found, and no unpublished data were submitted, regarding carcinogenicity for any of the titanium complexes. However, rats with Jensen sarcoma were treated with injections of Titanium Citrate in an anti-tumorigenicity study. Three-week survival rates were 88% and 39% for test and control groups, respectively.

In a skin irritation study involving New Zealand White rabbits (number not stated), an undiluted Isopropyl Titanium Triisostearate trade name material was classified as non-corrosive. Black iron oxide with 2% Isopropyl Titanium Triisostearate did not induce skin irritation (intact or abraded skin) in a study involving 6 New Zealand white rabbits. The topical application of titanium salicylates (concentration not stated) to the skin of rabbits did not cause skin irritation. In an SIOPT, skin irritation was not observed in any of the 23 subjects patch-tested with a concealer containing 0.4% Isopropyl Titanium Triisostearate (used as a surface modifier).

An eye powder containing 1.4% Isopropyl Titanium Triisostearate was evaluated for skin sensitization potential in an HRIPT using 101 subjects. The product tested was neither an irritant nor a sensitizer. Isopropyl Titanium Triisostearate did not function as a surface modifier in this eye powder. In another HRIPT (108 subjects), a foundation containing 0.433% Isopropyl Titanium Triisostearate (used as a surface modifier) was classified as a non-sensitizer. The skin sensitization potential of a foundation containing 0.4% Isopropyl Titanium Triisostearate (use as a surface modifier) was evaluated in a maximization test involving 26 healthy subjects (24 females and 2 males). Because the product contains volatile ingredients, it was allowed to air-dry for approximately 15 minutes prior to application. No adverse reactions were observed during induction and there were no instances of contact allergy during the challenge phase. Neither skin irritation nor sensitization was observed in an HRIPT (108 subjects) on a foundation containing 0.348% Isopropyl Titanium Triisostearate (used as a surface modifier). HRIPTs on 3 leave-on products containing 0.276%, 0.281%, and 0.337% Isopropyl Titanium Triisostearate (used as a surface modifier) were performed using groups of 50 subjects (1 per product tested). None of the 3 products induced allergic contact sensitization. A foundation topcoat containing 0.102% Isopropyl Titanium Triisostearate (used as a surface modifier) was evaluated for its sensitization potential in an HRIPT involving 101 subjects. There was no evidence of sensitization.

The results of a retrospective study involving 37 patients (all suspected of having titanium allergy) patch tested with 0.16% and 0.32% Titanium Citrate indicated a sensitization reaction in one patient at each concentration. In the same study, Titanium Citrate (up to 0.32%) did not induce sensitization in a group of 8 patients.

The phototoxicity of a pressed powder containing 0.004% Isopropyl Titanium Triisostearate was evaluated using 11 subjects. There was no evidence of phototoxicity.

The ocular irritation potential of 2 foundation topcoats containing 0.102% Isopropyl Titanium Triisostearate (used as a surface modifier) was evaluated using the EpiOcular™ human cell construct (reconstructed human cornea-like epithelium). When the 2 foundation topcoats were tested alone, t_{50} values of 15.4 h and > 24 h were reported. A 50:50 mixture of the 2 topcoats yielded a t_{50} of 15.2 h. The positive control (0.3% Triton®-X-100) yielded a t_{50} of 23.4 minutes. An Isopropyl Titanium Triisostearate trade name material was classified as non-corrosive in an ocular irritation study involving New Zealand White rabbits (number not stated). Black iron oxide with 2% Isopropyl Titanium Triisostearate was classified as a minimal ocular irritant in a study involving 6 New Zealand white rabbits.

The hemolytic activity of Titanium Citrate in human erythrocytes in vitro has been observed at concentrations ranging from 0.0025 to 0.8 mM. At a concentration of 0.8 mM, numerous erythrocytes ruptured, resulting in empty and retracted membranes (i.e., erythrocyte ghosts).

DISCUSSION

Five titanium complexes are being reviewed in this safety assessment. These ingredients are all tetravalent complexes of titanium, with a high degree of covalent character in the bonds between oxygen and titanium. However, Isopropyl Titanium Triisostearate appears to be unique, as it is a reaction product with colorant particles (forming a modified surface on those particles). Of the ingredients that are being reviewed, only Isopropyl Titanium Triisostearate is being used in cosmetic products. The results of a concentration of use survey conducted by the Council indicate that this ingredient is being used at concentrations up to 1.4% in leave-on products (eye shadows) and at concentrations up to 0.3% in rinse-off products (eye make-up removers). Furthermore, data provided by the Council indicate that Isopropyl Titanium Triisostearate functions only as a surface modifier in cosmetic products.

Available data on the method of manufacture demonstrate that, as a surface modifier in cosmetics, Isopropyl Titanium Triisostearate is covalently bound to a pigment (e.g., black iron oxide). Thus, the presence of any residual or unreacted Isopropyl Titanium Triisostearate in the product formulation would be considered an impurity. The Panel noted that if data are provided that indicate the presence of significant levels of residual Isopropyl Titanium Triisostearate when used as a surface modifier, 28-day dermal toxicity data and genotoxicity data would then be needed to evaluate the safety of this ingredient. The same would apply to any other identified use(s) of this ingredient that would yield free Isopropyl Titanium Triisostearate in the product formulation. In light of these considerations, the Panel requested confirmation of the following: (1) Isopropyl Titanium Triisostearate is only being used as a surface modifier, (2) the other titanium complex ingredients are not being used as surface modifiers, and (3) surface modification does not result in any appreciable residual Isopropyl Titanium Triisostearate in the final product. No data have been submitted to suggest that Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, or Titanium Salicylate are used in cosmetic formulations to modify pigment surfaces in this way. Therefore, the available information suggests that these four ingredients are discrete, unreacted complexes.

The Panel requested that, in addition to addressing their concerns relating to surface modifier chemistry, that industry determine the form of Isopropyl Titanium Triisostearate (bound to pigment or not) that is associated with the use concentration data that were provided. Also, the form of Isopropyl Titanium Triisostearate that was tested in the unpublished product formulation safety test data (included in this safety assessment) that were provided should be identified as well.

Additionally, the Panel determined that the available data are sufficient to arrive at a conclusion on the safety of Isopropyl Titanium Triisostearate when used as a surface modifier, but that additional data are needed for completion of the safety assessment of Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, and Titanium Salicylate. The complete list of data needs on these 4 ingredients includes:

- Maximum use concentrations
- Methods of manufacture
- Impurities
- 28-day dermal toxicity data; depending on the results of this study, additional systemic toxicity data may be needed
    - Depending on the results of these studies, various systemic toxicity data may also be needed
- Skin irritation and sensitization data at cosmetic use concentrations, except for Titanium Citrate

Skin irritation and sensitization data on Titanium Citrate are not needed because the Panel determined that results from a retrospective study on 37 patients (all suspected of having titanium allergy) patch tested with 0.16% and 0.32% Titanium Citrate are sufficient for evaluating these endpoints.

In response to the Panel's data requests, confirmation of whether or not Isopropyl Titanium Triisostearate was used as a surface modifier in the product formulation test data that were previously provided by the Council was received. With the exceptions of HRIPT data on an experimental product containing 1.4% Isopropyl Titanium Triisostearate, phototoxicity data (humans) on a pressed powder containing 0.0004% Isopropyl Titanium Triisostearate, and acute oral and dermal toxicity, genotoxicity, and skin and ocular irritation data on an Isopropyl Titanium Triisostearate trade name material (98% Isopropyl Titanium Triisostearate and < 2% isopropyl alcohol), the ingredient Isopropyl Titanium Triisostearate was used as a surface modifier in all of the studies that were provided by the Council. Confirmation that the Council's use concentration data on Isopropyl Titanium Triisostearate relate to the use this ingredient as a surface modifier was also received, as were additional HRIPT data on Isopropyl Titanium Triisostearate (used as a surface modifier). However, data relating to the presence of residual, unreacted Isopropyl Titanium Triisostearate in products in which this ingredient is being used as a surface modifier were not provided. Until these data are provided, whether or not the use concentration data represent the

bound ingredient or the bound + unreacted ingredient remains unknown. Information on whether or not the remaining ingredients in this safety assessment function as surface modifiers also has not been provided, neither were the remaining data on these ingredients that were requested by the Panel.

The only available impurities data are on tetraisopropyl titanate (a titanium compound used in the manufacture of Isopropyl Titanium Triisostearate) and on Isopropyl Titanium Triisostearate. These data indicate the presence of calcium (0.0003%) and titanium (16.99%), but not other metals or polychlorinated biphenyls and halogens, in tetraisopropyl titanate and < 2% isopropanol in Isopropyl Titanium Triisostearate. The Panel stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

CONCLUSION

The CIR Expert Panel concluded that Isopropyl Titanium Triisostearate is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when used as a surface modifier. The Panel also concluded that the data are insufficient to determine the safety of the following 4 ingredients: Titanium Citrate,* Titanium Ethoxide,* Titanium Isostearates,* and Titanium Salicylate.*

**Not reported to be in use.*

TABLES

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

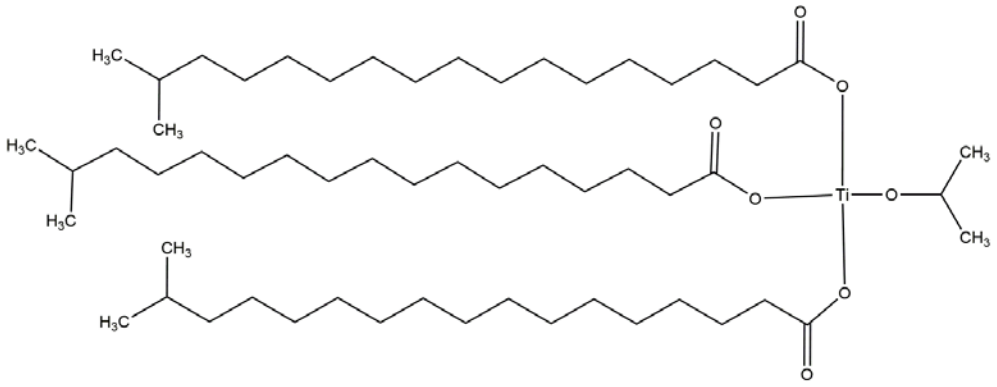
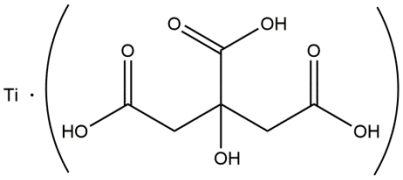
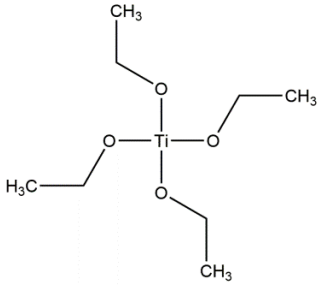
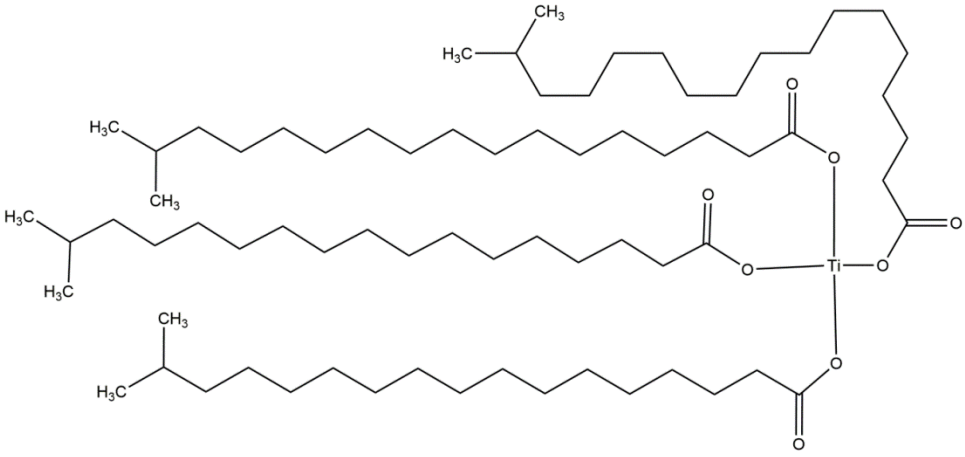
Ingredient CAS No.	Definition & Structures	Function(s)
Isopropyl Titanium Triisostearate 61417-49-0	Isopropyl Titanium Triisostearate is the organic compound that conforms to the formula:  [However, after modification of a colorant particle surface, the drawn isopropyl group would be replaced with a bond to the particle, as in Figure 3.]	Surface Modifiers
Titanium Citrate	Titanium Citrate is the salt of titanium and citric acid prepared by electrolysis. 	Colorants; Humectants
Titanium Ethoxide 3087-36-3	Titanium Ethoxide is the organic salt that conforms to the formula: 	Binders
Titanium Isostearates	Titanium Isostearates is the product formed by the reaction of titanium tetraethoxide and isostearic acid. 	Film Formers; Opacifying Agents

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

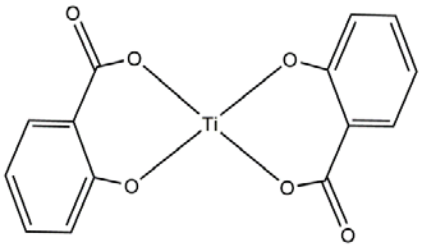
Ingredient CAS No.	Definition & Structures	Function(s)
Titanium Salicylate	Titanium Salicylate is the titanium salt of salicylic acid. 	Preservatives

Table 2. Chemical and Physical Properties of Titanium Complexes Ingredients

Property	Value/Results	Reference
Isopropyl Titanium Triisostearate		
Form	Reddish liquid	4
Odor	Waxy fatty acid	4
Molecular Weight (Da)	961.415 (for the unreacted, discrete complex; not as a coated colorant particle)	33
pH (solvent not stated)	5 - 6	4
Solubility	Insoluble in water; soluble in < 5% xylene	4
Viscosity (cps @ 77ºF)	125	4
Evaporation rate (relative to n-butyl acetate)	Slower	4
Boiling point (ºC)	149	4
Titanium Citrate		
Solubility	Soluble in water	2
Dissociation	Dissociation of free citrate increased with rise in pH (i.e., with increased alkalinity).	2
Titanium Ethoxide		
Form	white solid light-yellow liquid	34 3
Odor	Similar to alcohol	34
Molecular Weight (Da)	228.11	
Melting Point (ºC)	54	34
Flash Point (ºC)	42 to 43	3
Density (g/cm^3)	1.109	3
Vapor Pressure (hPa)	57.26	3
$\log K_{ow}$	- 0.3	3
Water solubility (mg/l)	789,000	3
Hydrolysis $t_{1/2}$ (min)	$\leq$ 3 to < 120	3
Titanium Salicylate		
Molecular Weight (Da)	320.08	35

Table 3. Frequency and Concentration of Use According to Duration and Type of Exposure.[8,9]

	Isopropyl Titanium Triisostearate	
	# of Uses	Conc. (%)
Totals/Conc. Range	**513**	**0.00002-1.4**
Duration of Use		
Leave-On	*506*	*0.00002-1.4*
Rinse off	*7*	*0.18-0.3*
Diluted for (bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	99	0.00002-1.4
Incidental Ingestion	253	0.08-0.42
Incidental Inhalation- Sprays	5[a];3[b]	NR
Incidental Inhalation- Powders	21;3[b]	0.25-0.75
Dermal Contact	229	0.0002-1.4
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	NR
Hair-Coloring	NR	NR
Nail	7	0.18
Mucous Membrane	257	0.08-0.42
Baby Products	NR	NR

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

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

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

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 4. Skin Irritation and Sensitization Studies on Titanium Complexes

Test Substance	Animals/Subjects/Cells	Test Protocol	Results
Irritation (Animal)			
Isopropyl Titanium Triisostearate trade name material (98% Isopropryl Titanium Triisostearate and < 2% isopropyl alcohol; not used as a surface modifier)	New Zealand white rabbits (number not stated)	Test substance (dose/cm^2 not stated) administered under semi-occlusive wrap for 4 h. Scores for erythema recorded at 4 h, 24 h, 48 h, and 72 h after patch removal	Primary dermal irritation scores: erythema (0.3), edema (0), and overall score (0.3). Test substance was non-corrosive.[17]
Black iron oxide with 2% Isopropyl Titanium Triisostearate (colorant particles surface modified with Isopropyl Titanium Triisostearate)	6 New Zealand white rabbits	Test substance (0.5 g, moistened with saline) applied for 24 h, under occlusive patch (5 cm^2), to intact and abraded sites on opposite sides of vertebral column. Patch was secured with hypoallergenic cloth tape. Reactions scored at 24 h and 72 h post-application. Mean irritation scores averaged to determine the PII (≥5 = skin irritant)	PII = 0. Test substance was non-irritating to abraded and intact skin.[22]
titanium salicylates (concentration not stated). Chemical structures not provided. Whether or not titanium salicylates is inclusive of discrete chemical (Titanium Salicylate, cosmetic ingredient) is unknown	Rabbits (number and strain not stated)	Protocol details not stated.	Test substance did not cause skin irritation.[16]
Irritation (Human)			
Concealer containing 0.4% Isopropyl Titanium Triisostearate (colorant particles surface modified with Isopropyl Titanium Triisostearate, i.e. use as a surface modifier)	23 subjects	SIOPT. Test substance (dose/cm^2 not stated)	Test substance did not cause skin irritation.[36]

Table 4. Skin Irritation and Sensitization Studies on Titanium Complexes

Test Substance	Animals/Subjects/Cells	Test Protocol	Results
Sensitization (Human)			
Foundation containing 0.348% Isopropyl Titanium Triisostearate (used as a surface modifier)	108 male and female subjects	HRIPT. During induction, occlusive patch containing product applied to upper back (patch dimensions and amount applied not stated; dose per cm^2 unknown). Induction phase (9 applications): Patches applied for 24 h to the same site on Mondays, Wednesdays and Fridays. Sites evaluated at 24 h after patch removal on Tuesdays and Thursdays, and at 48 h after patch removal on Saturdays. After non-treatment period (~ 2 weeks), challenge patch applied for 24 h to new site on back. Sites evaluated at 24 h, 48 h, and 72 h after patch removal.	No evidence of skin irritation or sensitization in any of the subjects tested.[27]
Eye powder containing 1.4% Isopropyl Titanium Triisostearate. (Isopropyl Titanium Triisostearate did not function as a surface modifier in this product.)	101 subjects	HRIPT. Finn chamber (occlusive patches). Product applied (20 µl or mg; dose per cm^2 not stated) for 48 h to one side of infrascapular area of back on Mondays, Wednesdays, and Fridays for 3 consecutive weeks (9 patch applications total). Challenge phase initiated after 2-week non-treatment period. Challenge patches applied for 48 h to induction site and a new site. Reactions scored at 48 h and 96 h post-application.	The product did not cause skin irritation or sensitization.[24]
Foundation containing 0.433% Isopropyl Titanium Triisostearate (used as a surface modifier)	108 subjects (males or females)	HRIPT. During induction, 2 cm x 2 cm occlusive patch containing product (0.2 ml or 2 g, or amount sufficient to cover patch) applied to infrascapular area of back or to upper arm. Nine induction applications: Patches applied for 24 h to same site on Mondays, Wednesdays, and Fridays for 3 consecutive weeks. Sites evaluated 24 h after patch removal, except for Monday evaluations after Friday removals. Ten- to 15-day non-treatment period before challenge. Occlusive 24-h challenge patch containing product applied to new test site. Sites evaluated at 48 h and 72 h after patch application.	No evidence of skin sensitization in any of the subjects tested. [25]
Foundation containing 0.4% Isopropyl Titanium Triisostearate (colorant particles surface modified with Isopropyl Titanium Triisostearate, i.e., use as a surface modifier)	26 subjects (24 females and 2 males)	Because product contains volatile ingredients, it was allowed to air-dry prior to application. Maximization test: Initially, 0.25% aqueous SLS (0.05 ml) applied for 24 h, under occlusive patch, to arm or back. Patch removal followed by re-application of SLS. Next, total of five 48-h (72 h, if over weekend) induction exposures, under occlusive patch, to product (at SLS site). During induction, each product application followed by 24 h SLS application. Challenge phase initiated after pre-treatment (1 h) of new site with 5% aqueous SLS (0.05 ml). Occlusive challenge patch then applied for 48 h to same site. Reactions evaluated at 15 to 30 min and 24 h after patch removal.	The product did not cause adverse reactions during induction, and there was no evidence of contact allergy after challenge patch application. Product did not possess detectable contact sensitizing potential.[26]

Table 4. Skin Irritation and Sensitization Studies on Titanium Complexes

Test Substance	Animals/Subjects/Cells	Test Protocol	Results
Leave-on product containing 0.337% Isopropyl Titanium Triisostearate (used as a surface modifier)	50 subjects	HRIPT. Induction: semi-occlusive patch containing product (0.2 ml) applied to unnamed site (patch dimensions not stated; dose per cm^2 unknown). Nine, 48-h applications over 3-week period. After 2-week non-treatment period, challenge patch applied for 24 h to new site. Sites evaluated at 24 h and 48 h. Same test procedure in 2 HRIPTs below.	None of the subjects had a low- or high-level reaction during induction or challenge. No evidence of allergic contact sensitization.[28]
Leave-on product containing 0.281% Isopropyl Titanium Triisostearate (used as a surface modifier)	50 subjects	HRIPT	None of the subjects had a low- or high-level reaction during induction or challenge. No evidence of allergic contact sensitization.[28]
Leave-on product containing 0.276% Isopropyl Titanium Triisostearate (used as a surface modifier)	50 subjects	HRIPT	None of the subjects had a low- or high-level reaction during induction or challenge. No evidence of allergic contact sensitization.[28]
Foundation topcoat containing 0.102% Isopropyl Titanium Triisostearate (colorant particles surface modified with Isopropyl Titanium Triisostearate, i.e., use as a surface modifier)	101 subjects	HRIPT. Induction: Semi-occlusive patch containing the product (0.2 ml) applied for 24 h to infrascapular area of back (to right or left of midline) or to upper arm. Total of 9 consecutive patch applications. Patches applied on Friday removed after 24 h, and application sites evaluated on following Monday (i.e., 72 h after patch application). After 10- to 15-day non-treatment period, challenge phase initiated during week 6 of study. Identical patches applied for 24 h to new test sites. Reactions scored at 48 h and 72 h post-application.	There was no evidence of skin sensitization.[29]

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2019 FDA VCRP Data

Isopropyl Titanium Triisostearate

03A - Eyebrow Pencil	5
03B - Eyeliner	8
03C - Eye Shadow	43
03D - Eye Lotion	5
03F - Mascara	24
03G - Other Eye Makeup Preparations	14
07A - Blushers (all types)	15
07B - Face Powders	21
07C - Foundations	41
07E - Lipstick	253
07F - Makeup Bases	4
07G - Rouges	5
07I - Other Makeup Preparations	48
08A - Basecoats and Undercoats	1
08E - Nail Polish and Enamel	4
08G - Other Manicuring Preparations	2
10E - Other Personal Cleanliness Products	4
12A - Cleansing	1
12C - Face and Neck (exc shave)	3
12F - Moisturizing	5
12H - Paste Masks (mud packs)	2
12J - Other Skin Care Preps	5
Total	**513**

Titanium Citrate - No Data

Titanium Ethoxide - No Data

Titanium Isostearates - No Data

Titanium Salicylate - No Data

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 17, 2019

SUBJECT: Updated Concentration of Use Information: Organo-Titanium Ingredients (all uses reported are as a surface modifier)

Concentration of Use by FDA Product Category – Organo-Titanium Ingredients*

Isopropyl Titanium Triisostearate
Titanium Citrate
Titanium Ethoxide
Titanium Isostearates
Titanium Salicylate

Ingredient	Product Category	Maximum Concentration of Use**
Isopropyl Titanium Triisostearate	Eyebrow pencils (3A)	0.018-0.086%
Isopropyl Titanium Triisostearate	Eyeliners (3B)	0.02-0.92%
Isopropyl Titanium Triisostearate	Eye shadows (3C)	0.083-1.4%
Isopropyl Titanium Triisostearate	Eye lotions (3D)	0.01-0.012%
Isopropyl Titanium Triisostearate	Eye makeup removers (3E)	0.18-0.3%
Isopropyl Titanium Triisostearate	Mascara (3F)	0.00002-0.15%
Isopropyl Titanium Triisostearate	Other eye makeup preparations (3G)	0.086-0.36%
Isopropyl Titanium Triisostearate	Sachets (4D)	0.1%
Isopropyl Titanium Triisostearate	Blushers (7A)	0.02-0.56%
Isopropyl Titanium Triisostearate	Face powders (7B)	0.25-0.75%
Isopropyl Titanium Triisostearate	Foundations (7C)	0.00085-0.51%
Isopropyl Titanium Triisostearate	Lipstick (7E)	0.08-0.42%
Isopropyl Titanium Triisostearate	Makeup bases (7F)	0.046-0.056%
Isopropyl Titanium Triisostearate	Rouges (7G)	0.08%
Isopropyl Titanium Triisostearate	Makeup fixatives (7H)	0.01%
Isopropyl Titanium Triisostearate	Other makeup preparations (7I)	0.25-0.44%
Isopropyl Titanium Triisostearate	Basecoats and undercoats (manicuring preparations) (8A)	0.001%
Isopropyl Titanium Triisostearate	Nail polish and enamel (8E)	0.18%
Isopropyl Titanium Triisostearate	Face and neck products (12C) Not spray	0.0002-0.22%
Isopropyl Titanium Triisostearate	Body and hand products (12D) Not spray	0.005%
Isopropyl Titanium Triisostearate	Paste masks and mud packs (12H)	0.0023%
Isopropyl Titanium Triisostearate	Other skin care preparations (12J)	0.0006-0.13%
Isopropyl Titanium Triisostearate	Suntan products (13A) Not spray	0.28%

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

**Used as a surface modifier for all reported uses

Information collected in 2017
Table prepared December 14, 2017

Table updated December 7, 2018: added function; high concentration of mascara increased from 0.024% to 0.15%; other makeup preparations low concentration changed from 0.21% to 0.25%
Table updated January 17, 2019 All reported uses are as a surface modifier; maximum use concentration eye shadow changed from 1.5% to 1.4%

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: October 4, 2018

SUBJECT: Isopropyl Titanium Triisostearate

TKL Research. 2013. Repeated insult patch test study (foundation containing 0.433% Isopropyl Titanium Triisostearate used as a surface modifier).

Clinical Research Laboratories, Inc. 2013. Repeated insult patch test (foundation containing 0.348% Isopropyl Titanium Triisostearate used as a surface modifier).

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

TKL RESEARCH

REPEATED INSULT PATCH STUDY

Foundation containing 0.433% Isopropyl Titanium Isostearate used as a surface modifier

TKL STUDY NO. DS102413-2

CONDUCTED FOR:

[redacted]

DATE OF ISSUE:

June 14, 2013

Version 1.0

201.587.0500 • www.tklresearch.com

TKL Research, Inc. 365 West Passaic Street, Rochelle Park, NJ 07662

TABLE OF CONTENTS

APPENDICES

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

Jonathan S. Dosik, MD
Dermatologist
Principal Investigator

6/11/13
Date

Kathleen Georgeian
Director, Dermatologic Safety Testing

6/13/13
Date

Michelle Medina
Manager, Dermatologic Safety Testing

6/13/13
Date

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

TITLE OF STUDY

Repeated Insult Patch Study

SPONSOR

[redacted]

STUDY MATERIALS

Formula No.	Batch No.	Product Description
[redacted]	13121948	[redacted]

DATE STUDY INITIATED

April 1, 2013

DATE STUDY COMPLETED

May 10, 2013

DATE OF ISSUE

June 14, 2013

INVESTIGATIVE PERSONNEL

Jonathan S. Dosik, MD - Dermatologist
Principal Investigator

Kathleen Georgeian
Director, Dermatologic Safety Testing

Michelle Medina
Manager, Dermatologic Safety Testing

CLINICAL SITE

TKL RESEARCH, INC
48 South Franklin Turnpike
Ramsey, NJ 07446

SUMMARY

Product [redacted], was evaluated neat to determine its ability to sensitize the skin of volunteer subjects with normal skin using an occlusive repeated insult patch study. One hundred eight (108) subjects completed the study.

Under the conditions employed in this study, there was no evidence of sensitization to product, [redacted]

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 100 completed subjects. In the absence of any sensitization reactions in this sample size (100 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 3.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females, 18 years of age or older, in general good health;
2. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events (AEs);
3. Were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. Had completed a medical screening procedure; and
5. Had read, understood, and signed an informed consent (IC) agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. Had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. Had psoriasis and/or active atopic dermatitis/eczema;
4. Were females who were pregnant, planning to become pregnant during the study, or breast-feeding; and/or
5. Had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated.

3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. Patches were applied on Mondays, Wednesdays, and Fridays for 3 consecutive weeks. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2]

Following the 9th evaluation, the subjects were dismissed for a Rest Period of approximately 10-15 days.

Subjects who were absent once during the Induction Phase received a make-up (MU) patch at the last Induction Visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading). Subjects who missed the 9th evaluation (N9G) but have had 9 patch applications were considered to have completed the Induction Phase.

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Following a negative Induction, a 48/72-hour sequence of "-/+," "?/+," or "+/+"

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

resulted in an additional reading being performed at the 96-hour interval. Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during Induction, and a single application and 2 readings at Challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK 1

DAY	ACTIVITIES
1[3]	Staff obtained informed consent, reviewed completed medical screening form, applied patches
2	Subject removed patches
3	Staff graded sites, applied patches
4	Subject removed patches
5	Staff graded sites, applied patches
6	Subject removed patches

WEEK 2

1	Staff graded sites, applied patches
2-6	Same as Week 1

WEEK 3

1-6	Same as Week 2

WEEK 4

1	Staff graded sites; applied make-up (MU) induction patches, if required
2	Subject removed MU induction patches
3	Staff graded MU induction sites at MU visit
2-7	Rest Period

WEEK 5

1-7	Rest Period

WEEK 6

1	Staff applied patches
2	Subject removed patches
3	Staff graded sites
4	Staff graded sites

[3] Study flow starting with Week 1, Day 1, will be altered when enrollment occurs other than on Monday. Study flow could be altered when a holiday occurs during the study.

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

- = No reaction
? = Minimal or doubtful response, slightly different from surrounding normal skin
+ = Definite erythema, no edema
++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E = Marked/severe erythema
S = Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p = Papular response > 50%
pv = Papulovesicular response > 50%
D = Damage to epidermis: oozing, crusting and/or superficial erosions
I = Itching
X = Subject absent
PD = Patch dislodged
NA = Not applied
NP = Not patched (due to reaction achieved)
N9G = No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

Identification : [redacted]
Batch No. : 13121948
Amount Applied : 0.2 g

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the Sponsor, the study material was considered reasonably safe

for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material is kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the Sponsor and the disposition documented in the logbook.

4.3 Application of Study Material

All study material was supplied by the Sponsor. Material was applied in an amount proportionate to the patch type or as requested by the Sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm. Unless otherwise directed by the Sponsor, the study material was discarded upon completion of the study.

4.4 Description of Patch Conditions

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch is secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pad is affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the Challenge Phase of a Repeated Insult Patch Test (RIPT) than that seen during Induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the Challenge Phase is generally similar to that seen during Induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. TKL's preferred Rechallenge procedure involves the application of the product to naive sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under

both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the Sponsor's review on the premises of TKL.

7.0 RESULTS AND DISCUSSION

One hundred fourteen (114) subjects between the ages of 21 and 70 were enrolled and 108 completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II). The following table summarizes subject enrollment and disposition:

Number enrolled:		114
Number discontinued:		6
Lost to follow-up:	2	
Voluntary withdrawal:	4	
Number completed:		108

Source: Table 1, Appendix I

There were no AEs reported during the study.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to product, [redacted].

9.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

Draize JH, Woodward G, Calvary HO. Methods for the study of irritation and toxicology of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 1944; 82: 377-390.

Lanman BM, Elvers WB, Howard CS. The role of human patch testing in a product development program. Joint Conf Cosmet Sci Toilet Goods Assoc 1968; 135-145.

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Zhai H, Maibach HI. Dermatotoxicology. 6th ed. New York:Hemisphere, 1996.

Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980: 41-53.

Griffith JF. Predictive and diagnostic testing for contact sensitization. Toxicol Appl Pharmacol, Suppl 1969; 3:90.

Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

[redacted]

APPENDIX I

SUMMARY TABLES

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	114
Subjects completed induction phase	108 (94.7)
Subjects completed all phases	108 (94.7)
Total subjects discontinued	6 (5.3)
Lost to follow-up	2 (1.8)
Voluntary withdrawal	4 (3.5)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	28 (24.6)
N (%) 45 to 65	76 (66.7)
N (%) 66 and up	10 (8.8)
Mean (SD)	50.2 (11.0)
Median	50.3
Range	21.2 to 70.6
Gender	
N (%) Male	15 (13.2)
N (%) Female	99 (86.8)
Race	
Asian	4 (3.5)
Black	7 (6.1)
Caucasian	96 (84.2)
Hispanic	7 (6.1)

See data listing 2 for further detail.

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[redacted] TKL Study No. DS102413

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = Formula # [redacted]

	Induction Reading										Challenge Phase		
Response	1	2	3	4	5	6	7	8	9	Make Up	48hr	72hr	96hr(*)
-	111	106	103	102	104	104	102	103	103	14	107	108	
?	1	2	4	3	2	2	3	3	3	1	1	0	
+	1	3	1	2	1	2	2	1	1	0	0	0	
Total evaluable	113	111	108	107	107	108	107	107	107	15	108	108	
Number absent	0	2	5	3	3	1	2	1	1		0	0	
Number discontinued	1	1	1	4	4	5	5	6	6		6	6	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=108)

Response	n(%) Subjects
-	102 (94.4%)
?	1 (0.9%)
+	5 (4.6%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

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TKL Study No. DS102413

Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

APPENDIX II

DATA LISTINGS

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
002	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
003	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
004	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
005	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
006	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
007	04/01/13	04/01/13	--	04/12/13	I3	S	12
008	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
009	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
010	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
011	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
012	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
013	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
014	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
015	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
016	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
017	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
018	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
019	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
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021	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
022	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
023	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
024	04/01/13	04/01/13	--	04/10/13	I3	S	10
025	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
026	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
027	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
028	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
029	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
030	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
031	04/01/13	04/01/13	--	04/05/13	I0	L	5

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
033	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
034	04/01/13	04/01/13	--	04/10/13	I3	S	10
035	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
036	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
037	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
038	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
039	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
040	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
041	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
042	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
043	04/01/13	04/01/13	--	04/22/13	I7	L	22
044	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
045	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
046	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
047	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
048	04/01/13	04/01/13	05/07/13	05/10/13	C	C	40
049	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
050	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
051	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
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060	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
061	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
062	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
063	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
064	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
065	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
066	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
067	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
068	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
069	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
070	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
071	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
072	04/03/13	04/03/13	--	04/17/13	I5	S	15
073	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
074	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
075	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
076	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
077	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
078	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
079	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
080	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
081	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
082	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
083	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
084	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
085	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
086	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
087	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
088	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
089	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
090	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
091	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
092	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
093	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

Generated on 05/16/13:12:01 by DISPLIST.SAS / Uses: DEMOGS, RESPONSE, FINAL

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
094	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
095	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
096	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
097	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
098	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
099	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
100	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
101	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
102	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
103	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
104	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
105	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
106	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
107	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
108	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
109	04/03/13	04/03/13	05/07/13	05/10/13	C	C	38
110	04/05/13	04/05/13	05/07/13	05/10/13	C	C	36
111	04/05/13	04/05/13	05/07/13	05/10/13	C	C	36
112	04/05/13	04/05/13	05/07/13	05/10/13	C	C	36
113	04/05/13	04/05/13	05/07/13	05/10/13	C	C	36
114	04/05/13	04/05/13	05/07/13	05/10/13	C	C	36

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

Generated on 05/16/13:12:01 by DISPLIST.SAS / Uses: DEMOGS, RESPONSE, FINAL

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Race
001	58.5	Female	Black
002	48.7	Female	Caucasian
003	57.0	Female	Caucasian
004	22.6	Female	Caucasian
005	55.2	Female	Caucasian
006	43.7	Female	Caucasian
007	48.4	Female	Hispanic
008	54.4	Female	Caucasian
009	59.7	Female	Caucasian
010	45.6	Female	Black
011	54.3	Female	Caucasian
012	55.0	Female	Asian
013	41.4	Female	Hispanic
014	47.9	Female	Caucasian
015	66.7	Male	Caucasian
016	47.2	Female	Caucasian
017	45.9	Female	Caucasian
018	57.6	Male	Caucasian
019	40.5	Female	Hispanic
020	52.8	Male	Caucasian
021	49.1	Female	Caucasian
022	53.4	Female	Caucasian
023	21.2	Male	Caucasian
024	68.3	Female	Hispanic
025	70.3	Male	Caucasian
026	52.3	Male	Caucasian
027	62.4	Female	Caucasian
028	61.9	Female	Black
029	53.5	Female	Caucasian
030	58.3	Female	Caucasian
031	60.7	Female	Caucasian
032	23.3	Female	Caucasian
033	56.0	Female	Caucasian
034	58.9	Female	Caucasian
035	46.2	Female	Caucasian
036	46.2	Female	Caucasian
037	22.3	Female	Caucasian

Generated on 05/16/13:12:01 by DEMOLIST.SAS / Uses: DEMOGS

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Race
038	41.0	Female	Caucasian
039	53.4	Female	Black
040	46.2	Female	Caucasian
041	55.6	Male	Caucasian
042	36.6	Female	Caucasian
043	42.0	Female	Hispanic
044	58.9	Female	Caucasian
045	41.7	Male	Caucasian
046	58.6	Female	Caucasian
047	69.1	Female	Caucasian
048	48.6	Female	Caucasian
049	28.8	Female	Hispanic
050	68.2	Female	Caucasian
051	63.6	Female	Caucasian
052	59.2	Male	Caucasian
053	47.8	Female	Caucasian
054	52.5	Female	Caucasian
055	57.1	Female	Caucasian
056	49.9	Female	Caucasian
057	68.3	Female	Caucasian
058	62.2	Female	Caucasian
059	59.3	Female	Caucasian
060	51.6	Female	Caucasian
061	25.9	Female	Caucasian
062	58.9	Female	Caucasian
063	44.7	Female	Caucasian
064	55.8	Female	Caucasian
065	49.0	Female	Caucasian
066	62.7	Female	Caucasian
067	57.9	Female	Caucasian
068	47.4	Female	Caucasian
069	45.7	Female	Caucasian
070	60.9	Female	Caucasian
071	47.1	Female	Asian
072	30.4	Female	Hispanic
073	49.6	Female	Caucasian
074	47.5	Female	Caucasian

Generated on 05/16/13:12:01 by DEMOLIST.SAS / Uses: DEMOGS

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Race
075	50.3	Female	Caucasian
076	36.1	Female	Caucasian
077	35.6	Female	Asian
078	39.6	Female	Caucasian
079	61.1	Female	Caucasian
080	48.6	Female	Caucasian
081	54.1	Female	Caucasian
082	54.1	Female	Caucasian
083	32.3	Female	Caucasian
084	70.6	Female	Caucasian
085	55.5	Female	Caucasian
086	49.8	Female	Caucasian
087	55.3	Female	Caucasian
088	67.4	Female	Caucasian
089	67.5	Female	Caucasian
090	43.0	Male	Caucasian
091	47.4	Female	Caucasian
092	41.2	Female	Caucasian
093	51.1	Female	Caucasian
094	50.2	Female	Caucasian
095	49.2	Female	Caucasian
096	31.2	Female	Asian
097	47.7	Female	Black
098	67.3	Female	Caucasian
099	48.5	Male	Caucasian
100	56.2	Female	Caucasian
101	56.6	Male	Black
102	47.1	Female	Caucasian
103	41.9	Female	Caucasian
104	53.7	Female	Black
105	55.9	Male	Caucasian
106	25.8	Male	Caucasian
107	49.8	Female	Caucasian
108	52.7	Female	Caucasian
109	42.2	Female	Caucasian
110	32.4	Female	Caucasian
111	39.1	Female	Caucasian
112	56.6	Female	Caucasian
113	49.2	Male	Caucasian
114	42.2	Female	Caucasian

Generated on 05/16/13:12:01 by DEMOLIST.SAS / Uses: DEMOGS

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = Formula [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
001	-	-	-	-	-	-	-	-	-		-	-	
002	-	-	-	-	-	-	-	-	-		-	-	
003	-	-	-	-	-	-	-	-	-		-	-	
004	-	-	-	-	-	-	-	-	-		-	-	
005	-	-	-	-	-	-	-	-	-		-	-	
006	-	-	-	-	-	-	-	-	-		-	-	
007	-	-	-	X	X	X	X	X	X		X	X	
008	-	+	?	?	?	?	?	?	?		-	-	
009	-	-	-	-	-	-	-	-	-		-	-	
010	-	-	-	-	-	-	X	-	-	-	-	-	
011	-	-	-	-	-	-	-	-	-		-	-	
012	-	?	?	+	X	?	?	?	?	?	-	-	
013	-	-	-	-	-	-	X	-	-	-	-	-	
014	-	-	-	-	-	-	-	-	-		-	-	
015	-	-	-	-	-	-	-	-	-		-	-	
016	-	-	-	X	-	-	-	-	-	-	-	-	
017	-	-	X	-	-	-	-	-	-	-	-	-	
018	-	+	+	+	+	+	+	+	+		-	-	
019	-	-	-	-	-	-	-	-	-		-	-	
020	-	X	-	-	-	-	-	-	-	-	-	-	
021	-	-	-	-	-	-	-	-	-		-	-	
022	-	-	-	-	-	-	-	-	-		-	-	
023	-	-	-	-	-	-	-	-	-		-	-	

See Table 3.1 for Key to Symbols and Scores

MU = Make-up reading for missed induction visit

(*) When required
Generated on 05/16/13:12:01 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = Formula #[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	X	X	X	X	X	X		X	X	
025	-	-	-	-	-	-	-	-	-		-	-	
026	-	-	-	-	-	-	-	-	-		-	-	
027	-	-	-	-	-	-	-	-	-		-	-	
028	-	-	-	-	-	-	-	-	-		-	-	
029	-	-	-	-	-	-	?	-	-		-	-	
030	-	-	-	-	-	-	-	-	-		-	-	
031	X	X	X	X	X	X	X	X	X		X	X	
032	-	-	-	-	-	-	-	-	-		-	-	
033	-	-	-	-	-	-	-	-	-		-	-	
034	-	-	-	X	X	X	X	X	X		X	X	
035	-	-	-	-	-	-	-	-	-		-	-	
036	-	-	-	-	-	-	-	X	-	-	-	-	
037	-	-	-	-	-	-	-	-	-		-	-	
038	-	-	-	-	-	-	-	-	-		-	-	
039	-	-	-	-	-	-	-	-	-		-	-	
040	-	-	-	-	-	-	-	-	-		-	-	
041	-	-	-	-	-	-	-	-	-		-	-	
042	-	-	-	-	-	-	-	-	-		-	-	
043	-	-	-	-	-	-	-	X	X		X	X	
044	-	-	-	-	-	-	-	-	-		-	-	
045	-	-	-	-	-	-	-	-	-		-	-	
046	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 05/16/13:12:01 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = Formula # [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	-	-	-	-	-	-	-	-	-		-	-	
048	-	-	-	-	-	-	-	-	-		-	-	
049	-	-	-	-	-	-	-	-	-		-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	-	-	-	-	-	-	-		-	-	
052	-	-	-	-	-	-	-	-	-		-	-	
053	-	-	-	-	-	-	-	-	-		-	-	
054	-	-	-	-	-	-	-	-	-		-	-	
055	-	-	-	-	-	-	-	-	-		-	-	
056	?	+	?	?	?	+	+	?	?		-	-	
057	-	-	-	-	-	-	-	-	-		-	-	
058	-	-	-	-	-	-	-	-	-		-	-	
059	-	-	-	-	-	-	-	-	N9G		-	-	
060	-	-	-	-	-	-	-	-	-		-	-	
061	-	-	-	-	-	-	-	-	-		-	-	
062	-	-	-	-	-	-	-	-	-		-	-	
063	-	X	-	-	-	-	-	-	-	-	-	-	
064	-	-	-	-	-	-	-	-	-		-	-	
065	-	-	-	-	-	-	-	-	-		-	-	
066	-	-	-	-	-	-	-	-	-		-	-	
067	-	-	X	-	-	-	-	-	-	-	-	-	
068	+	?	?	?	-	-	-	-	-		?	-	
069	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 05/16/13:12:01 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = Formula # [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
070	-	-	-	-	-	-	-	-	-		-	-	
071	-	-	-	-	-	-	-	-	-		-	-	
072	-	-	-	X	-	X	X	X	X		X	X	
073	-	-	-	-	-	-	-	-	-		-	-	
074	-	-	-	-	-	-	-	-	-		-	-	
075	-	-	-	-	-	-	-	-	-		-	-	
076	-	-	-	-	-	-	-	-	-		-	-	
077	-	-	-	-	-	-	-	-	-		-	-	
078	-	-	X	-	-	-	-	-	-	-	-	-	
079	-	-	-	-	-	-	-	-	-		-	-	
080	-	-	-	-	-	-	-	-	-		-	-	
081	-	-	-	-	-	-	-	-	-		-	-	
082	-	-	-	-	-	-	-	-	-		-	-	
083	-	-	-	-	-	-	-	-	-		-	-	
084	-	-	-	-	-	-	-	-	-		-	-	
085	-	-	-	-	-	-	-	-	-		-	-	
086	-	-	-	-	-	-	-	-	-		-	-	
087	-	-	-	-	-	-	-	-	-		-	-	
088	-	-	-	-	-	-	-	-	-		-	-	
089	-	-	-	-	-	-	-	-	-		-	-	
090	-	-	-	-	-	-	-	-	-		-	-	
091	-	-	X	-	-	-	-	-	-	-	-	-	
092	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 05/16/13:12:01 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = Formula #[redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
093	-	-	-	-	-	-	-	-	-		-	-	
094	-	-	-	-	-	-	-	-	-		-	-	
095	-	-	-	-	-	-	-	-	-		-	-	
096	-	-	-	-	-	X	-	-	-	-	-	-	
097	-	-	-	-	-	-	-	-	-		-	-	
098	-	-	-	-	-	-	-	-	-		-	-	
099	-	-	-	-	-	-	-	-	-		-	-	
100	-	-	-	-	-	-	-	-	-		-	-	
101	-	-	-	-	-	-	-	-	-		-	-	
102	-	-	-	-	-	-	-	-	-		-	-	
103	-	-	-	-	-	-	-	-	-		-	-	
104	-	-	-	-	-	-	-	-	-		-	-	
105	-	-	-	-	-	-	-	-	-		-	-	
106	-	-	X	-	-	-	-	-	-	-	-	-	
107	-	-	-	-	-	-	-	-	-		-	-	
108	-	-	-	X	-	-	-	-	-	-	-	-	
109	-	-	-	-	X	-	-	-	-	-	-	-	
110	-	-	-	-	-	-	-	-	-		-	-	
111	-	-	-	-	X	-	-	-	-	N9G	-	-	
112	-	-	-	-	-	-	-	-	-		-	-	
113	-	-	-	-	-	-	-	-	-		-	-	
114	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 05/16/13:12:01 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Clinical
Research
Laboratories, Inc.

Final Report

Repeated Insult Patch Test

Foundation containing 0.348% Isopropyl Titanium Triisostearate used as a surface modifier

CLIENT: [redacted]

ATTENTION: [redacted]

TEST MATERIAL: [redacted]

CRL STUDY NUMBER: CRL54613

AUTHORIZED SIGNATURES:

Bruce E. Kanengiser, M.D.
President/Medical Director

Michael J. Muscatiello, Ph.D.
Executive Vice President/COO

Anita Lee Cham, M.D.
Dermatologist

REPORT DATE: September 13, 2013

371 Hoes Lane, Suite 100 • Piscataway, NJ 08854 • (732) 981-1616 • FAX (732) 981-0520

Clinical
Research
Laboratories, Inc.

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: CRL54613

Start Date: July 29, 2013

Completion Date: September 6, 2013

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted.

Karen Hayberg
Signature of QA Auditor

Sept 13, 2013
Date

Clinical Research Laboratories, Inc.

FINAL REPORT

REPEATED INSULT PATCH TEST

PURPOSE

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material.

INVESTIGATIVE SITE

Clinical Research Laboratories, Inc.
371 Hoes Lane, Suite 100
Piscataway, New Jersey 08854
732-981-1616

TEST MATERIAL

The following test material was provided by [redacted] and was received by Clinical Research Laboratories, Inc. on July 16, 2013:

Test Material	Test Condition	Patch Type
[redacted]	Neat	Occlusive*

The test material was coded with the following CRL identification number:

CRL54613

STUDY DATES

This study was initiated on July 29, 2013 and was completed on September 6, 2013.

* Occlusive Strip with Flexcon® (Strukmyer LLC, Mesquite,TX or equivalent)

Clinical Research Laboratories, Inc.

PANEL SELECTION

Each subject was assigned a permanent CRL identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix I). Subjects who met the following Inclusion Criteria and none of the Exclusion Criteria were impaneled:

Inclusion Criteria

a. Male and female subjects between the ages of 18 and 70 years;

b. Subjects who do not exhibit any skin diseases which might be confused with a skin reaction from the test material;

c. Subjects who agree to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;

d. Subjects who agree to refrain from getting patches wet during the course of the study;

e. Subjects willing to sign an Informed Consent in conformance with 21CFR Part 50: "Protection of Human Subjects;"

f. Subjects who have completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;

g. Subjects in generally good health who have a current Subject Profile/Medical History on file;

h. Subjects who are dependable and able to follow directions as outlined in the protocol.

Exclusion Criteria

a. Female subjects who are pregnant or nursing;

b. Subjects who report allergies to cosmetics, toiletries or personal care products;

c. Subjects who are currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;

d. Subjects exhibiting any skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.

TEST METHOD

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scoring Scale

0 No visible skin reaction
± Barely perceptible erythema
1+ Mild erythema
2+ Well defined erythema
3+ Severe erythema and edema
4+ Erythema and edema with vesiculation

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.

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RESULTS

This study was initiated with 117 subjects. Nine subjects discontinued study participation for reasons unrelated to the test material. A total of 108 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table 1.

CONCLUSION

Based on the test population of 108 subjects and under the conditions of this study, the test material identified as [redacted] # [redacted] did not demonstrate a potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.

Clinical Research Laboratories, Inc.

TABLE I

Summary of Dermal Scores

Test Material:	[redacted] # [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
1	Discontinued											
1R	0	0	0	0	0	0	0	0	0	0	X	0*
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	X	0	0	X*
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0

R = Replacement
X = Subject Absent
*Subject could not return for the 96 hour evaluation since it occurred on a weekend when Clinical Research Laboratories, Inc. was closed

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	[redacted] # [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0
30	Discontinued											
30R	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0

R = Replacement

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	[redacted] # [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
51	0	0	0	0	0	0	0	Discontinued				
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	Discontinued									
61	0	0	0	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	0	0	0	0	0	0	0
63	±	±	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	Discontinued						
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	Discontinued											
70R	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0

R = Replacement

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	[redacted] # [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
76	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	Discontinued				
80	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0
85	Discontinued											
85R	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	±	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	Discontinued		
98	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0

R = Replacement

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	[redacted] # [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
101	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0
108	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0
110	0	0	0	0	0	0	0	0	0	0	0	0
111	0	0	0	0	0	0	0	0	0	0	0	0
112	0	0	0	0	0	0	0	0	0	0	0	0
113	0	0	0	0	0	0	0	0	0	0	0	0

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Appendix I

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
1	EB	19617	64	F
1R	AL	21695	50	F
2	ES	18566	51	M
3	JD	11122	52	F
4	BW	17003	63	F
5	PG	13069	63	F
6	RD	28937	27	F
7	CN	31839	26	M
8	AV	29958	56	F
9	BW	26154	60	F
10	LS	29870	55	M
11	AK	22180	29	F
12	FA	29845	52	F
13	CJ	15710	41	F
14	JM	28964	28	M
15	MK	30147	61	M
16	DK	30090	19	M
17	EB	31663	44	F
18	JL	31849	24	M
19	JW	08904	54	F
20	PD	31534	43	F
21	TC	08095	48	F
22	TG	26041	29	F
23	BD	06915	60	F
24	MA	20331	55	F
25	AH	31498	19	F
26	AC	31086	54	F
27	DM	31861	61	F
28	BC	20385	48	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
29	LS	29285	55	F
30	VC	15022	57	F
30R	DL	19589	61	F
31	RG	31847	55	M
32	CM	00741	68	F
33	GS	20700	50	F
34	CD	22327	60	F
35	TD	25458	30	M
36	CB	29673	64	F
37	BP	31862	52	F
38	GM	10424	57	F
39	PP	24006	58	M
40	BA	22252	66	F
41	MV	24282	25	M
42	KC	09142	58	F
43	DV	24281	56	F
44	SJ	19825	36	F
45	MJ	22469	18	M
46	PO	28514	56	F
47	RM	31850	32	F
48	JD	31840	55	F
49	MD	29807	52	M
50	TB	31608	39	F
51	MS	31779	58	M
52	LB	29951	47	F
53	LR	09909	31	F
54	SL	31116	28	F
55	RJ	31857	22	F
56	AB	31838	19	F

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Appendix I

Subject Demographics (Continued)

Subject Number	Subject Initials	CRL ID #	Age	Sex
57	RD	31781	19	F
58	ML	31667	37	F
59	ML	20303	68	F
60	LG	28238	52	F
61	TT	31859	23	F
62	MS	29053	41	F
63	EB	30283	61	M
64	LG	31210	45	F
65	BH	19736	70	F
66	SH	26830	67	F
67	RM	07210	59	F
68	MD	22090	29	F
69	MJ	18224	27	F
70	MG	29467	34	F
70R	LP	15115	49	F
71	BC	30688	30	M
72	FG	27993	48	M
73	PT	31866	31	M
74	LA	16749	55	F
75	NA	24910	42	F
76	CT	31868	36	F
77	SB	28419	27	F
78	CG	31853	38	F
79	KJ	31854	29	F
80	JL	19741	41	F
81	BD	26850	70	F
82	RC	31248	20	M
83	JL	31000	48	F
84	LN	14920	57	F
85	MS	31445	56	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
85R	SC	25209	54	M
86	PW	28174	28	F
87	TB	27194	54	F
88	ME	01693	58	F
89	MJ	25659	49	F
90	FK	04033	64	M
91	JO	31851	18	M
92	LD	30765	51	F
93	HW	31547	32	F
94	WW	29700	52	M
95	MM	31843	45	F
96	JG	11304	66	F
97	JC	31712	49	F
98	KG	30932	29	F
99	MH	29639	62	F
100	AB	31146	45	F
101	JB	31110	51	M
102	JD	25273	24	F
103	CC	29059	27	F
104	JA	27930	20	M
105	MA	03833	57	F
106	VH	31115	31	F
107	JW	24346	57	F
108	KH	30793	46	F
109	TI	31682	49	F
110	AM	31844	22	F
111	MG	27437	30	F
112	BS	11177	22	F
113	OS	29248	32	F

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 7, 2018

SUBJECT: Isopropyl Titanium Triisostearate

Anonymous. 2018. Summaries of HRIPTs of products containing Isopropyl Titanium Triisostearate used as a surface modifier.

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2018

Summaries of HRIPTs of Products Containing Isopropyl Titanium Triisostearate Used as a Surface Modifier

Three leave-on products were tested undiluted in HRIPTs.

Product 1 contained 0.275525% Isopropyl Titanium Triisostearate as a surface modifier

Product 2 contained 0.28098% Isopropyl Titanium Triisostearate as a surface modifier

Product 3 contained 0.33731% Isopropyl Titanium Triisostearate as a surface modifier

The HRIPTs of the three products were conducted under the same conditions:

Occlusivity: Semi-occlusive
Dermatologist as investigator: Yes
No. of subjects completing the study: 50
No. of patches during induction phase: 9
Duration of patch: 48 hours
Location of challenge patch: Naïve site

Results of the three HRIPTS were the same:

No. of subjects exhibiting low level reaction during induction: 0
No. of subjects exhibiting high level reaction during induction: 0
No. of subjects exhibiting low level reaction during challenge: 0
No. of subjects exhibiting high level reaction during challenge: 0
Pass/fail: Pass
Comments: Did not induce allergic contact sensitization

ICDRG Reading scale		
Negative (-)	Zero	Absent
Dubious (?)	1	Mild Erythema
Positive (+)	2	Define Erythema
Positive (++)	3	Erythema, Edema, papules
Positive (+++)	4	Erytheme, edema, papules , vesicles

Description	Interpretation
No Skin changes in tested area	Negative
Faint, non palpable erythema	Doubtful reaction: most authors do not consider this reaction as proof sensitization.
Palpapable erythema, moderate edema, or infiltrate. Papules not present or scarce. Vesicles not present.	Weak reaction
Strong infiltrate. Numerous papules. Vesicles present.	Strong Reaction
Coalescing vesicles. Bullae. Ulceration.	Extreme reaction
Inflammation sharply limited to the exposed area. Lack of infiltrate. Small petechiae. Pustules. Eflorescences other than papules and vesicles.	Irritant reaction, this kind of reaction may cause many problems upon interpretation.

Details of Test Methodology and Results			
0	panelist discontinued due to reactions		
48 hrs	patch duration		
9	induction patches		
3	weeks induction		
2	week rest period		
Original and virgin site	challenge Patch		
24, 48 hr	challenge readings		
0.02ml	Amount of product applied		
Test Material Concentration/Dilution	As is /No Dilution		

Grading Scale interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Personal Care Products Council
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Memorandum

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

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

DATE: December 4, 2018

SUBJECT: Isopropyl Titanium Triisostearate

The studies (including the HRIPT containing 0.102% Isopropyl Titanium Triisostearate) associated with the memo (number 4) provided by the Council on April 9, 2018 were completed on products containing Isopropyl Titanium Triisostearate used as a surface modifier.

The product (containing 1.4% Isopropyl Titanium Triisostearate) tested in the HRIPT provided by the Council on May 8, 2018 (memo number 5) was an experimental product that was never marketed. In this product, Isopropyl Titanium Triisostearate did not function as a surface modifier.

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Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: September 18, 2018

SUBJECT: Draft Tentative Report: Safety Assessment of Titanium Complexes as Used in Cosmetics (draft prepared for the September 24-25, 2018 CIR Expert Panel meeting)

The Council respectfully submits the following comments on the draft tentative report, Safety Assessment of Titanium Complexes as Used in Cosmetics.

Key Issues

It is not clear why all of the ingredients are in one report as it does not seem appropriate to use data on one ingredient, e.g., Titanium Citrate, to support the safety of the other ingredients. This report should be limited to the lead ingredient, Isopropyl Titanium Isopropyl Triisostearate used as a surface modifier. If all of the ingredients are left in this report a justification for grouping should be added to the report.

The draft Discussion states that "the Panel noted the likelihood that any toxic effects of these ingredients would primarily be due to the titanium component." If this is true, perhaps the report should include some information on titanium?

Council submission number 8 includes a figure from Kobo Products, Inc. that shows the reaction of Isopropyl Titanium Triisostearate with the hydrophilic pigment surface. This reaction still needs to be described in the CIR report.

Genotoxicity; Irritation; Ocular Irritation - Council submission number 6 included a description of a trade name material Ken-React KR TTS (reference 4) and a summary of safety studies of Ken-React KR TTS (reference 13). The material tested in the studies described in reference 13 is the material described in reference 4. Therefore, in the Genotoxicity, Irritation and Ocular Irritation sections it is not correct to state that the composition of an Isopropyl Titanium Triisostearate trade name material was not stated.

Additional Considerations

Abstract - How does the CIR Expert Panel know the "intended" conditions of use? Safety of ingredients should be assessed under the "reported" conditions of use.

Summary - As the method of manufacture of Isopropyl Titanium Triisostearate is included in the Method of Manufacture section, the following sentence: "Methods of manufacture for the remaining titanium complexes in this safety assessment were not found." needs to be deleted from the Summary.

Draft Discussion - Why is the impurity analysis of tetraisopropyl titanate (used to make Isopropyl Titanium Triisostearate) relevant to the all of the ingredients in the report? Tetraisopropyl titanate was not reported to be used to make Titanium Citrate (the only other ingredient for which a method of manufacture was found).

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: January 25, 2019

SUBJECT: Tentative Report: Safety Assessment of Titanium Complexes as Used in Cosmetics (release date January 9, 2019)

The Council respectfully submits the following comments on the tentative report, Safety Assessment of Titanium Complexes as Used in Cosmetics.

Key Issue

Discussion - As a negative Ames assay has been provided for Isopropyl Titanium Triisostearate (not bound to pigment), it should be made clear that only genotoxicity data in a mammalian system would be needed if the ingredient was used not associated with pigment.

Additional Considerations

Abstract - How does the CIR Expert Panel know the "intended conditions of use in cosmetic formulations"? If this is referring to the reported functions of the ingredients, this sentence should be revised. Rather than referring to ingredient use, "intended conditions of use" refers to cosmetic product use, e.g., lipstick is used on the lips, not used like a deodorant.

Cosmetic Use - The updated concentration of use survey from the Council indicating all reported uses are for Isopropyl Titanium Triisosterate used as a surface modifier needs to be added to the report.

Dermal Irritation and Sensitization - The spelling "Sensitzation" needs to be correct in the section heading. Please see Council memo 10 for clarification of the form Isopropyl Titanium Triisostearate tested in the sensitization studies.

Summary - Please add the word "New" to "Zealand White rabbits"

Table 4 - The product with 1.4% Isopropyl Titanium Triisostearate was an experimental product (never marketed) that contained Isopropyl Titanium Triisostearate that was not bound to pigment.

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