Safety Assessment of Organo-Titanium Ingredients as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: May 11, 2018
Panel Date: June 4-5, 2018

The 2018 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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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: May 11, 2018
Subject: Draft Report on Organo-Titanium Ingredients

A Scientific Literature Review (SLR) on 5 Organo-Titanium Ingredients was issued on March 13, 2018. The following data, received from the Personal Care Products Council (Council) during the 60-day comment period, are attached: 1) use concentration data (organo*062018data1* and *organo062018data2*); 2) human skin irritation and maximization test data on products containing 0.4% Isopropyl Titanium Triisostearate (*organo062018data3*); 3) an *in vitro* ocular irritation assay and an HRIPT on foundation topcoats containing 0.102% Isopropyl Titanium Triisostearate (*organo062018data4*); and 4) a human phototoxicity test on a pressed powder containing 0.004% Isopropyl Titanium Triisostearate (*organo062018data4*). These data are summarized in the draft report. Comments on the SLR were received from the Council (*organo062018pcpc*), and have been addressed.

Also included in this package for your review are the Draft Report (*organo062018rep)*, CIR report history (*organo062018hist*), flow chart (*organo062018flow*), literature search strategy (organo*062018strat*), ingredient data profile (*organo062018prof*), and 2018 FDA VCRP data (*organo062018FDA*).

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should identify matters to be addressed in the Discussion, and then issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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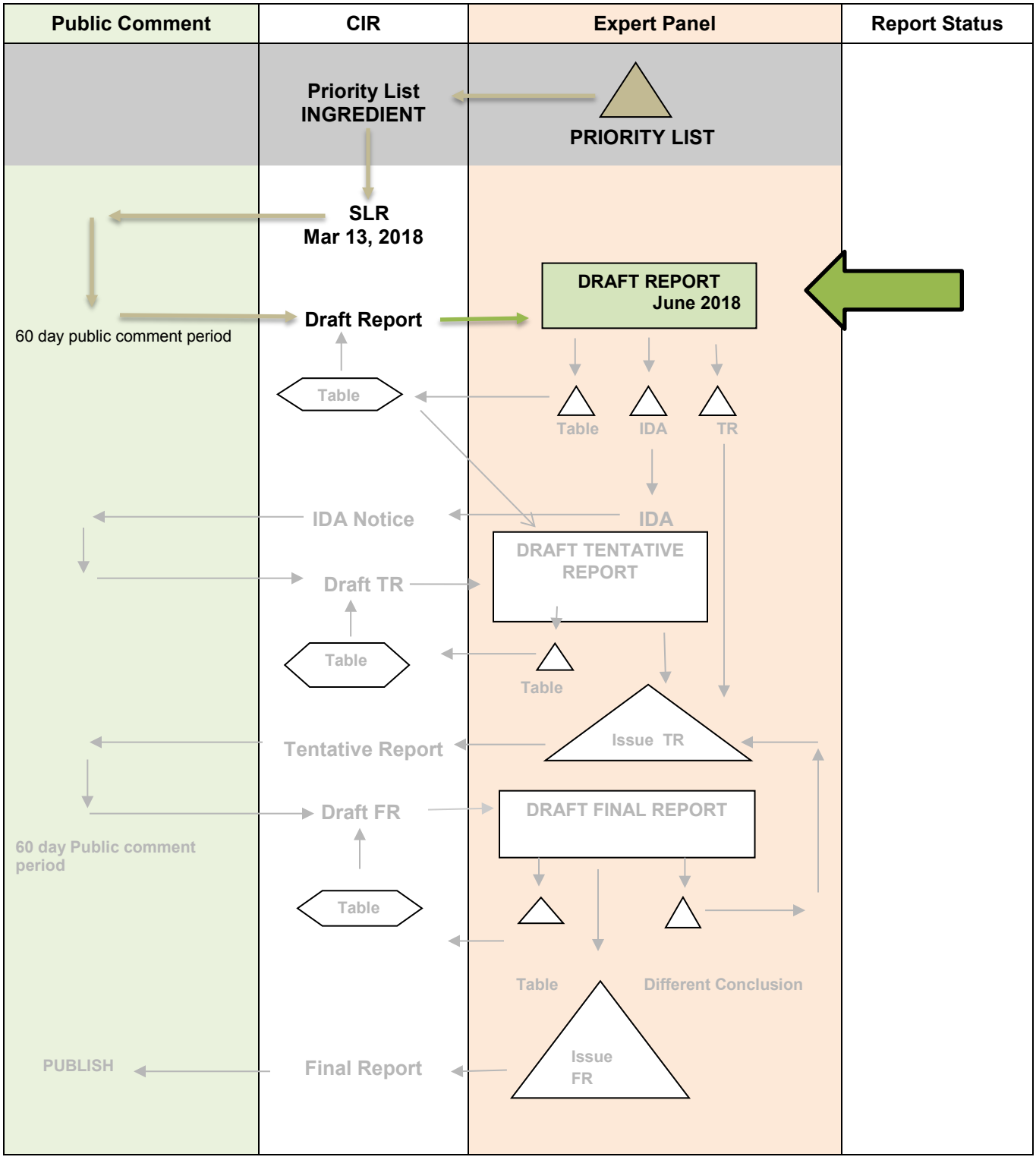
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Organo-Titanium Ingredients

MEETING June 2018



CIR History of:

Organo-Titanium Ingredients

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.

Data Profile on Organo-Titanium Ingredients for June 4th-5th, 2018 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					
Titanium Citrate						X															X										
Titanium Ethoxide												X																			
Titanium Isostearates																															
Titanium Salicylate										X			X	X									X								

X = data

[Organotitanium Ingredients–1/8/2018]

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

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INTRODUCTION

The safety of the following 5 organo-titanium ingredients as used in cosmetics is reviewed in this Cosmetic Ingredient Review (CIR) safety assessment.

Isopropyl Titanium Triisostearate
Titanium Citrate
Titanium Ethoxide
Titanium Isostearates
Titanium Salicylate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*), these organo-titanium ingredients are reported to have the following 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) (See Table 1).[1]

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 (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

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 organometallic derivatives of titanium.

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

Figure 1. This formula represents organometallic derivatives of titanium.

However, when the oxidation state of titanium is 4+ or greater ("n+" $\geq$ 4 in Figure 1) the titanium-bonding character is likely to be more covalent than ionic. Accordingly, structures for those chemicals wherein the oxidation state of titanium is known to be 4+ or greater have been drawn with covalent-titanium bonds for the sake of convenience (Figure 2).

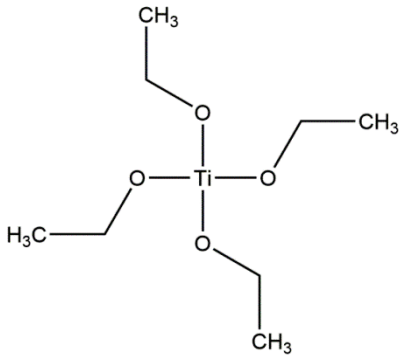


Figure 2. Titanium Ethoxide

Chemical and Physical Properties

Titanium Citrate and Titanium Ethoxide are soluble in water, and the latter ingredient has a density of 1.109.[2,3] Properties of these ingredients are presented in Table 2.

Method of Manufacture

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.[4] Exposure to air resulted in the quantitative oxidation of titanium (III) citrate to colorless titanium (IV) citrate.

Impurities

Impurities data on the organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

USE

Cosmetic

The safety of the organo-titanium ingredients is evaluated based on data received from the United States Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics.[5] 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.[6]

Only one of the organo-titanium ingredients is reported to be in use. According to 2018 VCRP data, Isopropyl Titanium Triisostearate is reported to be used in 580 cosmetic products (573 leave-on and 7 rinse-off products).[5] The results of a concentration of use survey conducted by the Council in 2017 indicate that Isopropyl Titanium Triisostearate is being used at concentrations up to 1.5% in leave-on products (eye shadows) and at concentrations up to 0.3% in rinse-off products (eye make-up removers).[6] Further use frequency and concentration of use data are presented in Table 3.

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 United States.[7]

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 to1.5% 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.

Noncosmetic

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.[8] Titanium Ethoxide has also been used as a catalyst in the synthesis of *N*-acyl-*O*-ethyl-*N*,*O*-acetals.[9]

TOXICOKINETIC STUDIES

Dermal Penetration

Data on the dermal penetration of organo-titanium ingredients 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.[4] 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.[10] 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 the toxicokinetics of Titanium Salicylate.

TOXICOLOGICAL STUDIES

Data on titanium salicylates (definition not provided) are included in toxicity studies that are summmarized in some of the following sections, because the name suggests that the data may be relevant to the safety assessment of the cosmetic ingredient, Titanium Salicylate.

Acute Toxicity Studies

Oral

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 authors concluded that 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.[10] 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.[10] Details relating to the test protocol were not included.

Subchronic Toxicity Studies

Data on the subchronic toxicity of organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

Chronic Toxicity Studies

Data on the chronic toxicity of organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity of organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

Data on the genotoxicity of organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of organo-titanium ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

ANTI-TUMORIGENICITY STUDY

Titanium Citrate

The anti-tumorigenicity of Titanium Citrate in rats (number and strain not stated) was evaluated using 2 groups of 46 rats (strain not stated) with Jensen sarcoma.[11,10] 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.[12] 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.[13] 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 SENSITZATION STUDIES

Irritation

Data on titanium salicylates (definition not provided) are included in this section, because the name suggests that the data may be relevant to the safety assessment of the cosmetic ingredient, Titanium Salicylate.

Animal

Titanium Salicylate

The topical application of titanium salicylates to the healthy skin of rabbits (number and strain not stated) did not cause skin irritation. The test concentration and other details relating to the test protocol were not included.[10] Though the definition of titanium salicylates is not provided in this study or the following human study, it is possible that these data may be useful in evaluating the skin irritation potential of Titanium Salicylate.

Human

Isopropyl Titanium Triisostearate

The skin irritation potential of a concealer containing 0.4% Isopropyl Titanium Triisostearate (undiluted) was evaluated in a 24 h single insult occlusive patch test (SIOPT) involving 23 subjects.[14] The application site and dose per cm^2 were not included. Skin irritation was not observed in any of the subjects tested.

Sensitization

Human

Isopropyl Titanium Triisostearate

The skin sensitization potential of a foundation containing 0.4% Isopropyl Titanium Triisostearate was evaluated in a maximization test involving 26 healthy subjects (24 females and 2 males).[15] Because the product contains volatile ingredients, it was allowed to air-dry for approximately 15 minutes prior to application. Initially 0.25% aqueous sodium lauryl sulfate (SLS, 0.05 ml) was applied for 24 h, under an occlusive patch, to a designated site (not stated). After patch removal, SLS was reapplied to the same site. During induction, the air-dried product was applied (volume, application site, and cm^2 area not stated), under an occlusive patch, to the same site for 48 h (or 72 h when placed over a weekend), and the site was examined for signs of irritation after patch removal. If irritation was not observed, SLS (0.25% aqueous, under an occlusive patch) was reapplied to the same site for 24 h. This was followed by reapplication of a fresh induction patch containing the product to the same site. This sequence was repeated for a total of 5 induction exposures. The authors noted that the aim during the induction phase was to maintain, at least, a minimal degree of irritation in order to enhance penetration through the corneum barrier. No adverse or unexpected reactions were observed in any of the subjects during the induction phase.

Pre-treatment with SLS was also performed prior to challenge with the product. Approximately 0.05 ml of 5% aqueous SLS was applied for 1 h, under an occlusive patch (15 mm cotton disk), to a new site. The product was then applied for 48 h, under an occlusive patch, to the same site. After challenge patch removal, the application site was evaluated 15 to 30 minutes later, and, again, 24 h later. There was no evidence of contact allergy in any of the subjects at 48 h or 72 h after challenge patch application. The authors concluded that the concealer containing 0.4% Isopropyl Titanium Triisostearate did not possess a detectable contact-sensitizing potential and, thus, is not likely to cause contact sensitivity reactions under normal use conditions.[15]

A foundation topcoat containing 0.102% Isopropyl Titanium Triisostearate was evaluated for its sensitization potential in an HRIPT involving 101 subjects.[16] A semi-occlusive patch containing the product (0.2 ml) was applied for 24 h to the infrascapular area of the back (to right or left of midline) or to the upper arm. The induction phase consisted of 9 consecutive patch applications of the product. Patches applied on Friday were removed after 24 h, and application sites were evaluated on the following Monday (72 h after patch application). The induction phase was followed by a 10- to 15-day non-treatment period. The challenge phase began during week 6 of the study, and identical patches were applied for 24 h to new test sites. Reactions were scored at 48 h and 72 h post-application. There was no evidence of sensitization to the foundation topcoat containing 0.102% Isopropyl Titanium Triisostearate.

Photosensitization/Phototoxicity

Human

Isopropyl Titanium Triisostearate

The phototoxicity of a pressed powder containing 0.004% Isopropyl Titanium Triisostearate was evaluated using 11 subjects.[17] The light source was a Xenon arc Solar Simulator (150W) with a continuous spectrum in the UVA-UVB range (290 to 400 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 (320 to 400 nm) using a filtered light source; irradiation was followed by ½ minimal erythemal dose (MED) of UVB (290 to 320 nm). 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 (290 to 320 nm). 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 was evaluated using the EpiOcular™ human cell construct (reconstructed human cornea-like epithelium).[18] 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. 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 provided.

SUMMARY

The safety of 5 organo-titanium ingredients as used in cosmetics is reviewed in this CIR safety assessment. According to the Dictionary, these organo-titanium ingredients are reported to have the following 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).

According to 2018 VCRP data, Isopropyl Titanium Triisostearate is reported to be used in 580 cosmetic products (573 leave-on and 7 rinse-off products). The results of a concentration of use survey conducted in 2017 indicate that Isopropyl Titanium Triisostearate is being used at concentrations up to 1.5% in leave-on products (eye shadows) and at concentrations up to 0.3% in rinse-off products (eye make-up removers).

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. Methods of manufacture for the remaining organo-titanium ingredients in this safety assessment were not found.

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. Data on titanium salicylates relating to short-term oral toxicity, systemic toxicity, and skin irritation potential are included in some of the study summaries below.

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. Chronic toxicity studies on the organo-titanium ingredients reviewed in this safety assessment were not found in the published literature.

The topical application of titanium salicylates (concentration not stated) to the healthy skin of rabbits or humans did not cause skin irritation. In a SIOPT, skin irritation was not observed in any of the 23 subjects patch-tested with a concealer containing 0.4% Isopropyl Titanium Triisostearate.

The skin sensitization potential of a foundation containing 0.4% Isopropyl Titanium Triisostearate 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. A foundation topcoat containing 0.102% Isopropyl Titanium Triisostearate was evaluated for its sensitization potential in an HRIPT involving 101 subjects. There was no evidence of sensitization.

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 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.

Rats with Jensen sarcoma were treated with injections of Titanium Citrate in an anti-tumorigenicity study, and 3-week survival rates were 88% and 39% for test and control groups, respectively.

The hemolytic activity of Titanium Citrate in human erythrocytes *in vitro* has been observed at concentrations ranging from 0.0025 to 0.4 mM.

TABLES

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

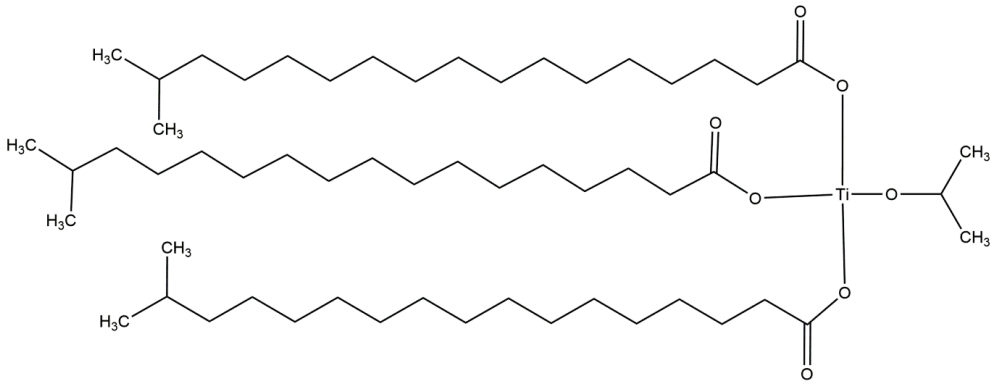
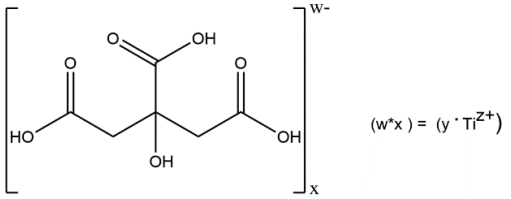
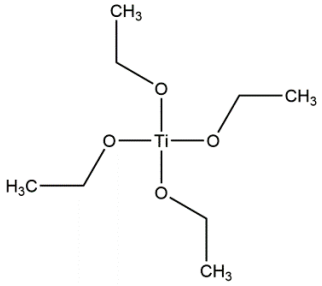
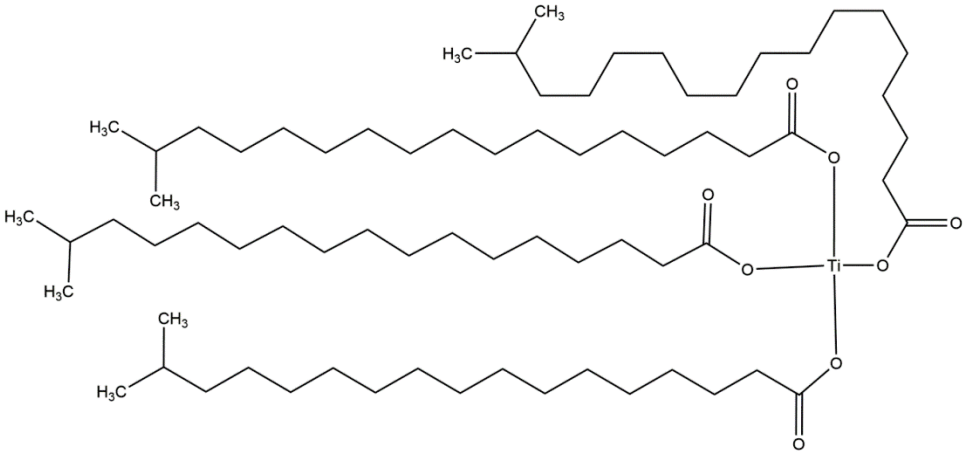
Ingredient CAS No.	Definition & Structures	Function(s)
Isopropyl Titanium Triisostearate 61417-49-0	Isopropyl Titanium Triisostearate is the organic compound that conforms to the formula: 	Surface Modifiers
Titanium Citrate	Titanium Citrate is the salt of titanium and citric acid prepared by electrolysis. 	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

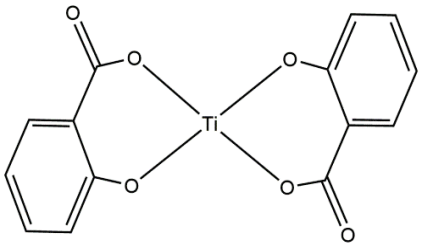


Table 2. Chemical and Physical Properties of Organo-Titanium Ingredients

Property	Value/Results	Reference
Isopropyl Titanium Triisostearate		
Molecular Weight (g/mol)	961.415	19
Titanium Citrate		
Solubility	Soluble in water	2
Dissociation	Dissociation of free citrate increased with rise in pH (i.e., increased alkalinity).	2
Titanium Ethoxide		
Form	white solid light-yellow liquid	20 3
Odor	Similar to alcohol	20
Formula Weight (Da)	228.11	
Melting Point (ºC)	54	20
Flash Point (ºC)	42 to 43	3
Density (g/cm^3)	1.109	3
Vapor Pressure (hPa)	57.26	3
logK_{ow}	- 0.3	3
Water solubility (mg/l)	789,000	3
Hydrolysis	Hydrolysis half-life = < 3 minutes to < 2 h.	3
Titanium Salicylate		
Molecular Weight (g/mol)	320.08	21

Table 3. Frequency and Concentration of Use According to Duration and Type of Exposure.[5,6]

	Isopropyl Titanium Triisostearate	
	# of Uses	Conc. (%)
Totals/Conc. Range	580	0.00002-1.5
Duration of Use		
Leave-On	573	0.00002-1.5
Rinse off	7	0.0023-0.3
Diluted for (bath) Use	NR	NR
Exposure Type		
Eye Area	100	0.00002-1.5
Incidental Ingestion	271	0.08-0.42
Incidental Inhalation- Sprays	5*	NR
Incidental Inhalation- Powders	20	0.25-0.75
Dermal Contact	279	0.0002-1.5
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	NR
Hair-Coloring	NR	NR
Nail	7	0.001-0.18
Mucous Membrane	275	0.08-0.42
Baby Products	NR	NR

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

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

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.

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2018 FDA VCRP Data

Isopropyl Titanium Triisostearate

03A - Eyebrow Pencil	8
03B - Eyeliner	8
03C - Eye Shadow	42
03D - Eye Lotion	6
03F - Mascara	23
03G - Other Eye Makeup Preparations	13
07A - Blushers (all types)	13
07B - Face Powders	20
07C - Foundations	86
07E - Lipstick	271
07F - Makeup Bases	3
07G - Rouges	31
07I - Other Makeup Preparations	30
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	4
Total	**580**

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: December 14, 2017

SUBJECT: Concentration of Use by FDA Product Category: Organo-Titanium Ingredients

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	0.083-1.5%
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	0.00002-0.024%
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	0.21-0.44%
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.

Information collected in 2017
Table prepared December 14, 2017

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: April 9, 2018

SUBJECT: Studies on Products Containing Isopropyl Titanium Triisostearate

Anonymous. 2006. Human Patch Test: Concealer containing 0.4% Isopropyl Titanium Triisostearate.

KGL Inc. 2006. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (foundation containing 0.4% Isopropyl Titanium Triisostearate).

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

Study Ref. No.: C06-0140
Patch Date: February 13, 2006

HUMAN PATCH TEST

1. TEST MATERIAL: Concealer 1006274[redacted] containing 0.4% Isopropyl Titanium Triiso stearate
   CPTC NO.: C06-0140.02
2. CONTROL MATERIAL: Concealer 1001572[redacted]
   CPTC NO.: C06-0140.03
3. TEST PROCEDURE:

   Single-Insults (24 hr.) X Occlusive Patch X Semi-Occlusive Patch _____
4. CONCENTRATION:

   Full-Strength X Aqueous _____ Solution _____ Dispersion _____ Aqueous Paste _____
   Other: _____

   Volatiles were allowed to evaporate on the patch _____ Patch was hydrated just prior to application to skin _____
5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS*	*IRRITATION SCORE**									
		0	±	1	1+	2	2+	3	3+	4	P.I.I.
Concealer 1006274[redacted]	23	23	0	0	0	0	0	0	0	0	0.00
Concealer 1001572[redacted]	23	23	0	0	0	0	0	0	0	0	0.00

6. CONCLUSIONS:

   A There were no significant differences in irritancy observed between the Test Material (s) and the Reference Control (s). X
   B _____

Consulting Dermatologist

* SCORE
0 = No evidence of any effect.
+ = (Barely Perceptible) = minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2 (Moderate) = Pink-red erythema visibly uniform in entire contact area.
3 (Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema.

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. - Primary Irritation Index - a value depicting the average skin response of the test panel as a whole. It is calculated by adding the Peak Irritation Score and dividing by the total number of test subjects.

KGL INC

FINAL REPORT dated April 3, 2006
KGL Protocol: #5999
Sample: Foundation [redacted]

www.kgl-inc.com or www.ivylabs.com

505 Parkway
Broomall, PA 19008-4204 (USA)

Telephone: [215] 387-8400
FAX: [215] 387-1046

E-mail address: ivystudies@verizon.net

Title: An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

Sponsor: [redacted]

Foundation containing 0.4% Isopropyl Titanium Triisostearate

Principal Investigator: Kays Kaidbey, M.D. (Board Certified Dermatologist)

Testing Facility: Ivy Laboratories (KGL, INC.)
505 Parkway
Broomall, PA 19008-4204 (USA)
(Phone: 215-387-8400)

Protocol: KGL Protocol #5999

Final Report Date: April 3, 2006

Kays Kaidbey, M.D.
Principal Investigator

April 3, 2006
Date

"The names of Ivy Laboratories (KGL, INC.), any officer, employee, or collaborating scientist are not to be used for any advertising, promotional or sale purposes without the written consent of Ivy Laboratories."

FINAL REPORT

KGL PROTOCOL:

Ivy Laboratories - KGL Protocol **#5999**

SPONSOR:

[redacted]

[redacted]

SPONSOR STUDY:

Authorization Letter Dated: February 15, 2006

STUDY TITLE:

Evaluation of the contact-sensitizing potential of a coded topically-applied test agent.

STUDY OBJECTIVE:

The objective of this study is to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

TEST MATERIAL:

The test sample, supplied by the sponsor, was a product labeled Foundation [redacted] and tested as supplied.

TEST PRODUCT ACCOUNTABILITY:

All test samples and materials were received in good condition by our Quality Assurance Department. The test materials and quantities were checked for (1) amount (2) product number or code (3) material container etc. The materials were individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). All test materials were stored under ambient conditions in an inaccessible location under the supervision of the investigator.

PRINCIPAL INVESTIGATOR:

Kays Kaidbey, M.D. (Board Certified Dermatologist)

Medical Director, KGL, INC.

Telephone: (215) 387-8400 (Ivy Labs)

FAX: (215) 387-1046

KGL ADMINISTRATIVE STRUCTURE:

Jane Chitwood (Screening, Patch Applications/Removals, Recognize AE's)

John B. Chicchi (Expert Grader)

Marie Windle (Panel Recruitment/Receptionist)

TESTING FACILITY:

Ivy Laboratories (KGL, INC.)

505 Parkway

Broomall, PA 19008-4204

CONDUCTION DATES:

This study was conducted from February 20, 2006 through March 24, 2006

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics. The criteria for exclusion were:

1 - History of sun hypersensitivity and photosensitive dermatoses

2 - History of drug hypersensitivity or recurrent dermatological diseases

3 - Pregnancy or mothers who are breastfeeding

4 – History of recurrent urticaria or hives

5 - Scars, moles or other blemishes over the test site which can interfere with the study

6 - Subjects receiving systemic or topical drugs or medications, including potential sensitizers within the previous 4 weeks

7 - Other medical conditions considered by the investigator as sound reasons for disqualification from enrollment into the study.

INFORMED CONSENT:

After the protocol, reasons for the study, possible associated risks and potential benefits or risks of the treatment had been completely explained, signed, informed subject

consent was obtained from each volunteer prior to the start of the study. Copies of all consent forms are on file at Ivy Laboratories (KGL, INC.).

METHOD:

Patches were applied to the upper outer arm, volar forearm or the back of each subject. The entire test was composed of two distinct phases: (1) an Induction phase and (2) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material was applied to the same site before the site was again covered with occlusive tape (induction patch). Since the test material [redacted] (Foundation) contained volatile ingredients, it was allowed to air-dry for approximately 15 minutes prior to application to the test site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS

pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Challenge Phase**:

After a ten day rest period which follows the last induction patch application, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm or side of back in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It

was then removed and the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded 15-30 minutes later and again 24 hours later for any reaction.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	GRADES:	CLASSIFICATION:
0 - 2/25	1	Weak
3 - 7/25	2	Mild

8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

RESULTS:

A total of twenty-seven (27) healthy, adult volunteers of both sexes who satisfied the inclusion criteria were enrolled into this study. There were 25 females and 2 males. Their ages ranged from 18 to 65 years. One subject #17 (initials F-D, a female) failed to return to the testing facility following the initial SLS patch and was lost to follow-up. She was subsequently dropped from the study. No test products were applied to this subject. The remaining 26 subjects completed this investigation as outlined in the standard protocol. The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Foundation [redacted] does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	C-A	23	F	C
02	J-C	35	F	C
03	ALB	44	F	C
04	CAW	44	F	C
05	S-G	38	F	C
06	EVI	18	F	C
07	T-B	59	M	C
08	C-M	52	F	C
09	D-D	44	F	C
10	E-S	23	F	C
11	K-K	45	F	C
12	J-G	45	F	C
13	L-M	46	F	C
14	A-D	39	F	C
15	M-D	47	F	C
16	G-S	28	F	C
17	F-D	63	F	C
18	M-F	51	F	C
19	K-M	45	F	C
20	N-B	56	F	C
21	K-D	22	F	C
22	J-F	58	F	C
23	C-B	20	F	C
24	A-C	32	F	C
25	M-C	41	F	C
26	R-K	54	F	C
27	J-C	65	M	C

C = Caucasian

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Foundation [redacted]

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	Dropped from the study	
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0
26	0	0
27	0	0

Challenge Readings:

48-Hour Reading – March 23, 2006
72-Hour Reading – March 24, 2006

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: April 23, 2018

SUBJECT: Studies on Products Containing Isopropyl Titanium Triisostearate

Institute for In Vitro Sciences. 2004. Tissue equivalent assay with Epiocular™ cultures (two foundation topcoats each containing 0.102% Isopropyl Titanium Triisostearate).

TKL Research. 1992. Phototoxicity test of a pressed powder containing 0.004% Isopropyl Titanium Triisostearate.

TKL Research. 2004. Human repeated insult patch test study of a foundation topcoat containing 0.102% Isopropyl Titanium Triisostearate.

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

FINAL REPORT

Study Title

TISSUE EQUIVALENT ASSAY WITH EPIOCULAR™ CULTURES

Test Articles

[redacted]

Authors

Hans Raabe, M.S.
David Hanobic, B.S.

Study Completion Date

12 August 2004

Performing Laboratory

Institute for In Vitro Sciences, Inc.
21 Firstfield Road, Suite 220
Gaithersburg, MD 20878

[redacted]

Study Number

[redacted]

Laboratory Project Number

[redacted]

TISSUE EQUIVALENT ASSAY WITH EPIOCULAR™ CULTURES

SUMMARY

IIVS Test Article Number	Sponsor's Designation	Concentration	t_{50}		pH
			Preliminary (23 March 2004)	Trial 1 (24 March 2004)	
[redacted]		neat	14.7 hours	15.4 hours	DpH
		neat	> 16 hours	> 24 hours	NCC
		50% / 50%	15.3 hours	15.2 hours	DpH
Positive Control	0.3% Triton®-X-100	NA	29.8 minutes	23.4 minutes	NA

DpH – Discolored pH paper; the pH could not be determined because the test article discolored the pH paper.
NCC – No Color Change; the pH could not be determined because the test article did not cause a color change that could be identified on the pH scale.
NA – Not Applicable

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The Tissue Equivalent Assay with EpiOcular™ Cultures of the test articles, [redacted] and [redacted], was conducted in compliance with the U.S. FDA Good Laboratory Practice Regulations as published in 21 CFR 58, the U.S. EPA GLP Standards 40 CFR 160 and 40 CFR 792, the UK GLP Compliance Programme, and the OECD Principles of Good Laboratory Practice in all material aspects with the following exceptions:

The identity, strength, purity and composition or other characteristics to define the test or control articles have not been determined by the testing facility.

The stability of the test or control articles under the test conditions has not been determined by the testing facility and is not included in the final report.

Analyses to determine the uniformity, concentration, or stability of the test or control mixtures, if applicable, were not performed by the testing facility.

Hans Raabe, M.S.
Study Director

12 August 2014
Date

QUALITY ASSURANCE STATEMENT

Study Title: Tissue Equivalent Assay with EpiOcular Cultures

Study Number: [redacted]

Study Director: Hans Raabe, M.S.

This study has been divided into a series of in-process phases. Using a random sampling approach, Quality Assurance monitors each of these phases over a series of studies. Procedures, documentation, equipment records, etc., are examined in order to assure that the study is performed in accordance with the U.S. FDA Good Laboratory Practice Regulations (21 CFR 58), the U.S. EPA GLP Standards (40 CFR 792 and 40 CFR 160), the UK GLP Compliance Programme and the OECD Principles of Good Laboratory Practice and to assure that the study is conducted according to the protocol and relevant Standard Operating Procedures.

The following are the inspection dates, phases inspected and report dates of QA inspections of this study:

Phase Inspected	Audit Date(s)	Reported to Study Director	Reported to Management
Protocol and Initial Paperwork	18-Mar-04	18-Mar-04	18-Mar-04
Rinsing of Tissues / Addition of MTT	25-Mar-04	26-Mar-04	26-Mar-04
Draft Report and Workbook	27-May-04	28-May-04	28-May-04
Final Report	11-Aug-04	11-Aug-04	12-Aug-04

This report describes the methods and procedures used in the study and the reported results accurately reflect the raw data of the study.

Amanda K. Ulrey, B.S.
Quality Assurance

12 August 2004
Date

SIGNATURE PAGE

TISSUE EQUIVALENT ASSAY WITH EPIOCULAR™ CULTURES

Initiation Date:	18 March 2004
Completion Date:	12 August 2004
Sponsor:	[redacted]
Sponsor's Representative:	[redacted]
Testing Facility:	Institute for In Vitro Sciences, Inc. 21 Firstfield Road, Suite 220 Gaithersburg, MD 20878
Archive Location:	Institute for In Vitro Sciences, Inc. Gaithersburg, MD 20878
Study Director:	Hans Raabe, M.S. — 12 August 2004 (Date)
Laboratory Management:	Greg Mun, B.A.

TEST ARTICLE RECEIPT

IIVS Test Article Number	Sponsor's Designation	Physical Description	Receipt Date	Storage Conditions*
[redacted]		light brown cream	4 March 2004	room temperature
		white cream	4 March 2004	room temperature

* - Protected from exposure to light

Test articles are 2 foundation topcoats of different shades, each with 0.102% isopropyl titanium triisostearate.

Each test material is tested alone, then a 50:50 mixture of the two test materials is tested.

TISSUE EQUIVALENT ASSAY WITH EPIOCULAR™ CULTURES

INTRODUCTION

The EpiOcular™ human cell construct (MatTek Corporation) was used to assess the potential ocular irritancy of the test articles. The MTT (3[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) conversion assay, which measures the NAD(P)H-dependent microsomal enzyme reduction of MTT (and to a lesser extent, the succinate dehydrogenase reduction of MTT) to a blue formazan precipitate, was used to assess cellular metabolism after exposure to a test article for various exposure times[1]. The duration of exposure resulting in a 50% decrease in MTT conversion in test article-treated EpiOcular™ human cell constructs, relative to control cultures, was determined (t_{50}).

The purpose of this study was to evaluate the potential toxicity of the test articles, supplied by [redacted] as measured by the conversion of MTT by EpiOcular™ human cell constructs after exposure to a test article for various exposure times. The laboratory phase of the study was conducted from 23 March 2004 to 25 March 2004 at the Institute for In Vitro Sciences, Inc. After a time range finding assay, the test articles were tested in a valid definitive assay to determine the time of exposure to a test article, which resulted in the t_{50} endpoint.

[1] Berridge, M.V., Tan, A.S., McCoy, K.D., Wang, R. (1996) The Biochemical and Cellular Basis of Cell Proliferation Assays That Use Tetrazolium Salts. **Biochemica** 4:14-19.

MATERIALS AND METHODS

Receipt of the EpiOcular™ Human Cell Construct Model

Upon receipt of the EpiOcular™ human cell construct kit, the solutions were stored as indicated by the manufacturer. The EpiOcular™ human cell constructs were stored at 2-8°C until used. On the day of dosing an appropriate volume of EpiOcular™ human cell construct Assay Medium was removed and warmed to approximately 37°C. Nine-tenths mL of Assay Medium were aliquoted into the wells of 6-well plates. The six-well plates were labeled to indicate test article and exposure time. The samples were inspected for air bubbles between the agarose gel and Millicell® insert prior to opening the sealed package. Cultures with air bubbles covering greater than 50% of the Millicell® area were not used. The 24-well shipping containers were removed from the plastic bag and their surfaces were disinfected with 70% ethanol. The EpiOcular™ human cell constructs were transferred aseptically into the 6-well plates. The EpiOcular™ human cell constructs were then incubated at 37±1°C in a humidified atmosphere of 5±1% CO_2 in air for at least one hour. The medium was aspirated and 0.9 mL of fresh Assay Medium were added to each assay well below the EpiOcular™ human cell construct. The plates were returned to the incubator until treatment was initiated.

Test Article Preparation

As instructed by the Sponsor, the test articles, [redacted], were tested neat. In addition, a third test article was prepared by mixing equal parts of the test articles, [redacted]. On the day of use in the exposure time range finding trial, 500 µL aliquots of each of the test articles, [redacted] were thoroughly mixed using a spatula, and then tested. On the day of the definitive trial, 1000 µL aliquots of each of the test articles, [redacted] were mixed and tested. The test article mixture will be referred to as [redacted] for the remainder of this report.

Assessment of Direct Test Article Reduction of MTT

Each test article was added to a 1.0 mg/mL MTT (Sigma) solution in warm Dulbecco's Modified Eagle's Medium (DMEM) containing 2 mM L-glutamine (MTT Addition Medium) to assess its ability to directly reduce MTT. Approximately 100 µL of each test article were added to 1 mL of the MTT solution and the mixtures were incubated in the dark at 37°C for approximately one hour. A negative control, 100 µL of sterile, deionized water (Quality Biological), was tested concurrently. If the MTT solution color turned blue/purple, the test article was presumed to have reduced the MTT. Water insoluble test materials may show direct reduction (darkening) only at the interface between the test article and the medium.

In cases where the test article was shown to reduce MTT, only those test articles that remained bound to the tissue after rinsing, resulting in a false MTT reduction signal, could present a problem. To evaluate whether residual test article was binding to the tissue and leading to a false MTT reduction signal, a functional check (using freeze-killed control tissue) was performed as described below in the section "Killed Controls (KC) for Assessment of Residual Test Article Reduction of MTT".

The test article, [redacted], was not observed to reduce MTT in the absence of viable cells.

The test articles, [redacted] were observed to reduce MTT spontaneously in the absence of viable cells. A killed control experiment was performed concurrently in the time range finding assay to determine the extent of the direct MTT reduction (if any) by the test articles alone.

pH Determination

The pH of each neat liquid test article was measured using pH paper. Initially, the neat test articles were added to pH paper (EM Science) with 0-14 pH range in 1.0 pH unit increments to approximate a narrow pH range. The pH could not be determined for the test article, [redacted], because the test article did not cause a color change that could be identified on the pH scale. The pH could not be determined for the test articles, [redacted] and [redacted], because the test article discolored the pH paper.

Time Range Finding Assay

A time range finding assay was performed to establish an appropriate exposure time range to be used in the definitive assay for each test article. Four exposure times of 1, 4, 8, and 16 hours were tested in the time range finding assay. One culture was treated per exposure time with 100 µL of the appropriate test article or control. Due to their viscous nature, a dosing device (flat-headed cylinder of slightly less diameter than the inner diameter of the tissue insert) was placed over the test articles, [redacted] to assure even spreading over the surface of the tissues. The negative control (exposure time control), 100 µL of sterile, deionized water, was exposed for 16 hours. The positive control, 100 µL of 0.3% Triton®-X-100 (Fisher), was exposed for 15 and 45 minutes (one culture per exposure time).

After the appropriate exposure time, the EpiOcular™ cultures were extensively rinsed with Calcium and Magnesium-Free Dulbecco's Phosphate Buffered Saline ($Ca^{++}Mg^{++}$-Free DPBS) and the wash medium was decanted. After rinsing, the tissue was transferred to 5 mL of Assay Medium for a 10 to 20 minute incubation at room temperature to remove any test article absorbed into the tissue. A 1.0 mg/mL solution of MTT in warm MTT Addition Medium was prepared no more than 2 hours before use. Three-tenths mL of MTT solution were added to designated wells in a prelabeled 24-well plate. The EpiOcular™ constructs were transferred to the appropriate wells after a second rinse with $Ca^{++}Mg^{++}$-Free DPBS. The trays were incubated at 37±1°C for approximately three hours in a humidified atmosphere of 5±1% CO_2 in air.

After the incubation period with MTT solution, the EpiOcular™ cultures were blotted on absorbent paper, cleared of excess liquid, and transferred to a prelabeled 24-well plate containing 2.0 mL of isopropanol in each designated well. The plates were sealed with parafilm and stored in the refrigerator (2-8°C) until the last exposure time was harvested. The plates were then shaken for at least two hours at room temperature.

At the end of the extraction period, the liquid within the Millicell® inserts was decanted into the well from which the Millicell® insert was taken. The extract solution was mixed and 200 µL were transferred to the appropriate wells of a 96-well plate. Two hundred µL of

isopropanol were added to the two wells designated as the blanks. The absorbance at 550 nm (OD_{550}) of each well was measured with a Molecular Devices Vmax plate reader.

Killed Controls (KC) for Assessment of Residual Test Article Reduction of MTT

To evaluate whether residual test article was binding to the tissue and leading to a false MTT reduction signal, a functional check (using freeze-killed control tissue) was performed. Freeze killed tissues were prepared by placing untreated EpiOcular™ constructs in the -20°C freezer overnight. The frozen tissues were allowed to thaw at least once at room temperature, and then placed back into the -20°C freezer at least overnight and were stored in the freezer until use.

For the test articles, [redacted] single killed tissues were treated with each test article in the normal fashion for the shortest and longest exposure times (1 and 16 hours). All assay procedures were performed exactly as described for the viable tissues. Although some residues of the test articles [redacted] were observed on the viable EpiOcular™ tissues after the rinsing and post-rinsing medium-soaking incubation, none were noted on the test article-treated killed control tissues. The negative control (100 µL of sterile, deionized water) was tested concurrently for 1 and 16 hours. A small amount of MTT reduction is expected from the residual NADH and associated enzymes within the killed tissue. This background reduction of MTT will be compared to the MTT reduction observed in the test article-treated killed-control tissues.

The raw OD_{550} value of the negative control-treated killed control was subtracted from the raw OD_{550} values for each of the test article-treated killed controls, to determine the net OD_{550} values of the test article-treated killed controls. The net OD_{550} values represent the amount of reduced MTT due to direct reduction by test article residues. For the test articles, [redacted] and [redacted] there was little or no direct MTT reduction measured in the test article-treated killed control compared to the negative control-treated killed controls.

Definitive Assay

Based on the results of the time range finding assay, four exposure times of 8, 16, 20, and 24 hours were chosen for the test articles, [redacted], in the definitive assay. The negative control (100 µL of sterile, deionized water) was exposed for 0.25, 4, 8, and 24 hours. The positive control (100 µL of 0.3% Triton®-X-100) was exposed for 15 and 45 minutes. The procedures used to conduct the definitive assay were essentially the same as for the time range finding assay with the exception that duplicate cultures were dosed per exposure time.

Presentation of Data

The raw absorbance values were captured. The mean OD_{550} value of the blank control wells was calculated. The corrected mean OD_{550} of the exposure time control(s) was determined by subtracting the mean OD_{550} of the blank control from their mean OD_{550}s. The corrected OD_{550} of the individual test article exposure times and the positive control exposure times was determined by subtracting the mean OD_{550} of the blank control from their OD_{550}s. All calculations were performed using an Excel spreadsheet. The following percent of control calculations were made:

$$\% \text{ of Control} = \frac{\text{corrected } OD_{550} \text{ of Test Article or Positive Control Exposure Time}}{\text{appropriate corrected mean } OD_{550} \text{ of Negative Control}} \times 100$$

Exposure time response curves were plotted with the % of Control on the ordinate and the test article or positive control exposure time on the abscissa. The t_{50} value was interpolated from each plot. To determine the t_{50}, the two consecutive points were selected, where one exposure time resulted in a relative survival greater than 50%, and one exposure time resulted in less than 50% survival. Two select points were used to determine the slope and the y-intercept for the equation $y=m(x) + b$. Finally, to determine the t_{50}, the equation was solved for $y=50$. If all of the exposure time points show greater than 50% survival, the t_{50} value is presented as greater than the maximum exposure time.

Criteria for a Valid Test

The assay results were accepted if the positive control, 0.3% Triton®-X-100, caused a t_{50} value within two standard deviations of the historical mean. The corrected mean OD_{550} value for the minimum negative control exposure time should be within 20% of the corrected mean OD_{550} value for the maximum negative control exposure time (up to 240 minutes).

RESULTS AND DISCUSSION

Time Range Finding Assay

A time range finding assay was performed, consisting of four exposure times of 1, 4, 8, and 16 hours for the test articles, [redacted] supplied by [redacted] The exposure time response curves are included in Appendix B. Based upon the results of the time range finding assay, four exposure times were selected for each test article for the definitive assay (see Materials and Methods). The t_{50} results for the time range finding assay are reported in Table 1, under "Preliminary".

The test article, [redacted] remained attached to the tissue following the rinsing and post-rinsing medium-soaking incubation process at all exposure times. The test article, [redacted] remained attached to the tissue following the rinsing and post-rinsing medium-soaking incubation process for the 16-hour exposure. The residual test article prolonged the test article exposure, which may have increased the toxicity to the treated tissues.

The test article, [redacted] was not observed to reduce MTT directly in the absence of viable tissue. However, the test articles, [redacted] were determined to reduce MTT spontaneously, and therefore, a killed-control experiment was performed concurrently in the exposure time range finding assay. Some residues of the test articles [redacted] were observed on the viable EpiOcular™ tissues after the rinsing and post-rinsing medium-soaking incubation, however, none were noted on the test article-treated killed control tissues. The negative control (100 µL of sterile, deionized water) was tested concurrently for 1 and 16 hours. The results of the killed control experiment showed that there was little or no direct MTT reduction measured in the test article-treated killed control compared to the negative control-treated killed controls. However, since no test article residues were observed on the killed control tissues (as were observed on the viable tissues), the results of the killed control test do not exclude the potential for direct MTT reduction by the test articles in the EpiOcular™ tissue constructs.

Definitive Assay

Four exposure times were treated in duplicate for each test article. The exposure times for the test articles, [redacted] were 8, 16, 20, and 24 hours. The negative control was also exposed in duplicate for 0.25, 4, 8, and 24 hours. Table 1 summarizes the t_{50} results of the definitive Tissue Equivalent Assay With EpiOcular™ Cultures for the test articles and the positive control, 0.3% Triton®-X-100, under "Trial 1". The exposure time response curves are included in Appendix B. Since the positive control fell within two standard deviations of the historical mean (15.2 – 39.2 minutes), and the corrected mean OD_{550} value for the minimum negative control exposure time (1.695) was within 20% of the corrected mean OD_{550} value for the maximum negative control exposure time (up to 240 minutes) (1.566), the assay results were accepted.

The test article, [redacted] remained attached to the tissue following the rinsing and post-rinsing medium-soaking incubation process at all exposure times. The test article, [redacted] remained attached to the tissue following the rinsing and post-rinsing medium-soaking incubation process for the 8, 20, and 24 hour exposures. The residual test article prolonged the test article exposure, which may have increased the toxicity to the treated tissues.

Table 1

IIVS Test Article Number	Sponsor's Designation	Concentration	t_{50}		pH
			Preliminary (23 March 2004)	Trial 1 (24 March 2004)	
[redacted]		neat	14.7 hours	15.4 hours	DpH
		neat	> 16 hours	> 24 hours	NCC
		50% / 50%	15.3 hours	15.2 hours	DpH
Positive Control	0.3% Triton®-X-100	NA	29.8 minutes	23.4 minutes	NA

DpH – Discolored pH paper; the pH could not be determined because the test article discolored the pH paper.
NCC – No Color Change; the pH could not be determined because the test article did not cause a color change that could be identified on the pH scale.
NA – Not Applicable

TKL RESEARCH, INC.

A Center for Clinical Trials

PHOTOTOXICITY TEST

TKL STUDY NO. [redacted]

CONDUCTED FOR:

[redacted]

DATE OF REPORT:

December 7, 1992

TKL Research, Inc. 4 Forest Avenue, Paramus, NJ 07652 (201) 587-0500 FAX (201) 587-0209

TITLE OF STUDY: Phototoxicity Test (1/2 MED)

SPONSOR: [redacted]

STUDY MATERIAL: [redacted] (Pressed Powder)

DATE INITIATED: October 5, 1992

DATE COMPLETED: October 8, 1992

REVISED PROCEDURE

DATE INITIATED: October 19, 1992

DATE COMPLETED: October 23, 1992

DATE OF REPORT: December 7, 1992

INVESTIGATIVE PERSONNEL:

Alan H. Greenspan, MD
Principal Investigator

Robert C. Reardon, PhD
Project Director

Edward K. Boisits, PhD
Director of Clinical Operations

Joy Taurozzi, RN
Clinical Study Coordinator

Maureen Damstra, BA
Clinical Evaluator

[redacted] [redacted] TKL Study No. [redacted]

INVESTIGATIVE PERSONNEL: (Cont'd.)

Esmirna Doherty
Clinical Evaluator

Myra Popowski
Clinical Assistant

CLINICAL SITE:

TKL Research, Inc.
4 Forest Avenue
Paramus, NJ 07652

[redacted] [redacted] TKL Study No. [redacted]

STATEMENT OF QUALITY ASSURANCE

All data and supporting documentation for this study have been audited by the TKL Quality Assurance Department and found to be accurate, complete and in compliance with all requirements of the protocol and TKL's Standard Operating Procedures. This report has been reviewed and accurately reflects all aspects of the conduct of the study.

All clinical research studies are performed by TKL Research, Inc. in accordance with federal regulations and proposed guidelines for good clinical practices which include:

21 CFR Part 52, Clinical Investigations

21 CFR Part 54, Obligations of Clinical Investigators of Regulated Articles

21 CFR Part 312, New Drug Product Regulations, Final Rule

21 CFR Part 50, Protection of Human Subjects

21 CFR Part 56, Standards for IRBs for Clinical Investigations

Susan Penna — Quality Assurance Manager

12/3/92 — Date

TKL Research, Inc. 4 Forest Avenue, Paramus, NJ 07652 (201) 587-0500 FAX (201) 587-0209

[redacted] [redacted] TKL Study No. [redacted]

SUMMARY

One (1) product, Product No. [redacted] was evaluated to determine its ability to induce a phototoxic reaction in the skin of normal volunteer subjects. Eleven subjects completed the study.

Under the conditions employed in this study, there was no evidence of phototoxicity to Product No. [redacted] a pressed powder containing 0.004% isopropyl titanium triisosterarate.

1.0 INTRODUCTION

1.1 OBJECTIVE

The purpose of this study was to determine whether the study material was capable of inducing a phototoxic skin reaction using a controlled photopatch evaluation procedure.

1.2 RATIONALE

Substances intended for topical application to human skin need to be evaluated for their propensity to irritate and/or sensitize. Once appropriate pre-clinical safety evaluation and routine human patch testing (e.g., prophetic or repeated insult patch tests) have been performed, it may be useful to obtain further information on possible phototoxic reactions.

Phototoxic reactions represent the most common form of photosensitivity. The exact mechanism of action is not understood, but is generally believed to be non-allergic (non-immunologic).

In a phototoxic reaction, a combination of light and the chemical-tissue (skin) complex cause a clinical reaction sometimes described as an "exaggerated ordinary sunburn." The chemical may reach the skin by a topical or systemic route. The specific wavelengths of light required to evoke a photosensitivity reaction are known as the action spectrum. This is approximately the same as the absorption spectrum of the photosensitizing substance. Most phototoxic reactions have an action spectrum in the UVA (320-400 nm) range and may even extend into the visible light region (400-700 nm). There are probably different types of phototoxic reactions depending upon the nature of the chemical (including dosage and route of administration), wavelengths and quantity of light exposure, as well as host tissue responses. Because an increasing number of individuals are being exposed to chemicals followed by light exposure, it has become important to screen substances for phototoxicity potential if the absorption spectrum of these chemicals and/or methods of use cause theoretical concern. Although there may be "immediate" and "delayed" types of phototoxic reactions, the method herein described is designed to detect both types of reactions. An immediate phototoxic reaction may appear within several hours of exposure, peak by 24 hours, and resolve within 48 to 96 hours. A delayed reaction may not begin until 24 hours, peak at 48 hours, and resolve very slowly over one (1) to two (2) weeks.

1.3 BACKGROUND

One (1) product was evaluated for phototoxicity using a study group of 10 volunteer subjects. On the basis of information provided by the Sponsor, this product was considered reasonably safe for evaluation on human subjects.

1.4 INSTITUTIONAL REVIEW BOARD

Before initiation of this study, the protocol and informed consent were reviewed and approved by the Institutional Review Board of TKL Research, Inc. on September 24, 1992.

2.0 STUDY MATERIAL

2.1 STORAGE, HANDLING AND DOCUMENTATION OF STUDY MATERIAL

Upon arrival of the material used in this study at TKL Research, Inc., receipt was documented in a general log book which serves as a permanent record of the receipt, storage and disposition of all study materials. A sample of the study material was reserved and stored for a period of six (6) months. At the conclusion of the clinical study, the remaining study material was returned to the Sponsor and the disposition documented in the log book. All information regarding the receipt, storage and disposition of the study material was also recorded on a Clinical Material Record form (see Appendix III) which is incorporated in this study report. All study materials are kept in a locked product storage room accessible to clinical staff members only.

2.2 NATURE OF STUDY MATERIAL

Product Identification	:	[redacted]
Description	:	Beige Powder
Quantity Provided	:	2 x 16 oz
Amount Applied	:	0.5 g
Special Instructions	:	Patch was wet with 0.2 ml of distilled water prior to applying product.

2.3 PATCH DEFINITION

Occlusive: Non-porous, plastic film adhesive bandage with a 2 cm x 2 cm Webril pad affixed with hypo-allergenic tape such as Scanpor or Micropore as needed.

3.0 EXPERIMENTAL DESIGN

3.1 STUDY GROUP SELECTION (See Demographics - Appendix II)

3.11 INCLUSION CRITERIA

1. Individuals 18 years of age or older.
2. Individuals with fair, uniformly colored skin on the lower thoracic area of the back which would allow a discernible erythema.
3. Individuals free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results.
4. Individuals who had completed a phototesting Medical Screening form as well as a Medical/Personal History form.
5. Individuals who had read, understood and signed an informed consent agreement.

3.12 EXCLUSION CRITERIA

1. Individuals with any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluations.
2. Individuals with a known sensitivity to cosmetics, skin care products or topical drugs as related to the product being evaluated.
3. Individuals who were under treatment for asthma.
4. Individuals with psoriasis and/or active atopic dermatitis/eczema.
5. Individuals taking medication which, in the opinion of the investigative personnel, would have interfered with study results.
6. Individuals taking medication known to cause photobiological reactions (i.e., tetracyclines, thiazides, etc.).
7. Individuals with cataracts.
8. Individuals with diabetes.
9. Females who were pregnant, planning a pregnancy or nursing a child.
10. Individuals with a history of skin cancer.

3.2 INFORMED CONSENT

A properly-executed informed consent document in compliance with FDA regulations (21 CFR 50) was obtained from each subject prior to entering the study. The signed informed consent is maintained in the study file. In addition, the subject was provided with a copy of the informed consent. A sample of the consent agreement is included as Appendix IV.

3.3 LIGHT SOURCE*

A Xenon Arc Solar Simulator (150W) was used which has a continuous emission spectrum in the UVA-UVB range (290 to 400 nm). A UVB absorbing filter (WG 320) which eliminated erythemogenic wavelengths (below 320 nm) was used for UVA dosing and removed for UVA/UVB dosing. The output was monitored at the beginning and periodically throughout each irradiation day using the Robertson-Berger Meter.

* All subjects wore UV protective goggles while being irradiated.

3.4 PROCEDURE

Minimal Erythemal Dose (MED) is defined as the time of light exposure required to produce a minimally-perceptible erythema reaction 16 to 24 hours after irradiation using a standardized ultraviolet light source that emits UVB (290-320 nm) as part of its emission spectrum. Subjects who are candidates for this evaluation will have skin types, commonly referred to as Fitzpatrick skin types, of Category I, II or III according to the following definitions:

Category I	Always burns easily, never tans
Category II	Always burns easily, tans minimally
Category III	Burns moderately, tans gradually (light brown)
Category IV	Burns minimally, always tans well (moderate brown)
Category V	Rarely burns, tans very well (moderate brown)
Category VI	Never burns, deeply pigmented

On Day One, an area (other than the study sites) approximately 5 cm x 2.5 cm was divided into a number of equal sites, irradiated and underlined with a surgical marker. The anticipated MED was estimated from the skin type (I, II or III) of the individual and the irradiation times calculated were based on the required energy output of the Xenon lamp to achieve a minimal erythema reaction. Each of the sites was irradiated with full spectrum UVL (UVB plus UVA) for exposure times which differ by a factor of 1.25, i.e., each irradiated site received 25% more exposure than the previous site. Sixteen to 24 hours later, the MED was determined by establishing the site which exhibited the least amount of perceptible erythema.

The products were applied to two (2) separate sites (irradiated site and non-irradiated site).

Approximately 24 hours after application, the patches were removed. One (1) set of sites was irradiated with 24 J/cm^2 of UVA (320-400 nm) irradiation using a filtered light source followed by 1/2 MED of UVB (290-320 nm). The other set of sites served as a non-irradiated control. One additional area was irradiated with 24 J/cm^2 of UVA irradiation followed by 1/2 MED of UVB (290-320 nm) as stated above and served as the irradiated control.

After reviewing the results, protocol deviations regarding the use of 24 J/cm^2 of UVA irradiation as opposed to the required 16 J/cm^2 and a difference in symbols used to record reactions were discovered. Another study was conducted as described using different subjects, 16 J/cm^2 of UVA irradiation followed by ½ MED of UVB and the scoring scale described in Section 3.5.

All sites were evaluated after patch removal and 24 and 48 hours following irradiation.

3.5 GRADING RESPONSES

All reactions were graded using the following symbols to express the response observed at the time of examination:

0 = No Visible Redness
1 = Mild Reaction - Faint Definitely Pink
2 = Moderate Reaction - Definite Redness, similar to sunburn.
3 = Severe Reaction - Very Intense Redness

Descriptions of Reactions*:

e = Questionable Swelling
E = Definite Swelling
p = Very Red, Pinpoint Evaluations
P = Many Red, Solid Pinpoint Evaluations, Granular feeling throughout the entire patch area.
v = Possibly some fluid build-up in the papules. Appear translucent at the top of the papules.
V = Blister containing Fluid. They will be a few millimeters to a centimeter in diameter.
s = Reaction appears to be beyond the patch site.
S = Reaction spreading well passed patch site. Reaction is the same both in and outside patch area.
B = Bullous reaction - Large elevation usually containing fluid. This fluid swelling will generally cover the entire patch test site. It can be composed of one (1) to several blisters from one (1) to several centimeters in diameter.
D = Oozing, crusting and/or superficial erosions.

3.6 EVALUATION OF RESPONSES

It is TKL's objective to have one evaluator perform all evaluations in a given study. However, substitution of one evaluator by another may occur during lunch periods or in the event of unexpected personal circumstances. All TKL evaluators have satisfied a formal certification requirement which is documented in TKL records and establishes their ability to conduct dermatological gradings. This assures that minimal differences occur in grading among evaluators.

4.0 DATA SUMMARY

See Computer Data: Individual Reaction Scores - Appendix I.

* Lower case designations were circled when recorded on the Case Report Form.

5.0 INTERPRETATION

See Working Criteria: Appendix V.

6.0 DOCUMENTATION AND RETENTION OF DATA

Case report forms supplied by TKL Research were designed to identify each subject, the products evaluated and the reactions observed. Originals or copies of all case report forms, source documents and reports will be kept on hard-copy file at TKL Research, Inc. in a secured room accessible only to TKL employees for a minimum of five (5) years from completion of the study. They are available for the Sponsor's review on the premises of TKL Research, Inc.

7.0 RESULTS & DISCUSSION

One (1) product, Product No. [redacted] was evaluated to determine its ability to induce a phototoxic reaction in the skin of normal volunteer subjects. Eleven subjects between the ages of 34 and 55 were enrolled and completed the study. After discovering a protocol deviation concerning a discrepancy in the number of joules used for UVA irradiation and a difference in symbols used to record reactions, the study was conducted again using different subjects. Eleven subjects between the ages of 23 and 71 were enrolled and completed the second study.

Under the conditions employed in this study, there was no evidence of phototoxicity to Product No. [redacted] a pressed powder containing 0.004% isopropyl titanium triisostearate.

8.0 SIGNATURES

PREPARED BY:

Robert C. Reardon, PhD
Project Director

REVIEWED AND APPROVED BY:

Joy Taurozzi, RN
Clinical Study Coordinator

Edward K. Boisits, PhD
Director of Clinical Operations

Susan Dennis, MA
Quality Assurance Manager

Alan H. Greenspan, MD
Principal Investigator

APPROVED BY:

Jon C. Anderson, PhD
President

[redacted]

APPENDIX I

COMPUTER DATA:

SUMMARY REACTION DATA
AND
INDIVIDUAL REACTION SCORES

KEY:

IRRAD STUDY MTL = Irradiated study material
NON-IRRAD STUDY MTL = Non-Irradiated study material
IRRAD CONTROL = Irradiated control

COMPANY: [redacted]

STUDY#: [redacted]

PROD#: [redacted]

TKL RESEARCH, INC.

DATA SUMMARY SHEET

PHOTOTOXICITY

EVALUATIONS USING 24J/CM^2

		24-HOUR READING			48-HOUR READING		
	SUBJECT#	IRRAD STUDY MTL	NON-IRRAD STUDY MTL	IRRAD CONTROL	IRRAD STUDY MTL	NON-IRRAD STUDY MTL	IRRAD CONTROL
1)	11379	1	0	1	0	0	0
2)	12883	1	0	1	0	0	1
3)	14005	1	0	1	1	0	1
4)	14638	1	0	1	0	0	0
5)	14918	2	0	2	2	0	2
6)	15426	1	0	1	0	0	1
7)	15685	0	0	0	0	0	0
8)	16197	0	0	1	0	0	0
9)	17600	1	0	1	0	0	1
10)	18537	0	0	1	0	0	1
11)	18791	1	0	1	1	0	1

[redacted]

COMPANY: [redacted]

STUDY#: [redacted]

PROD#: [redacted]

TKL RESEARCH, INC.

DATA SUMMARY SHEET

PHOTOTOXICITY

EVALUATIONS USING 16J/CM^2

		24-HOUR READING			48-HOUR READING		
	SUBJECT#	IRRAD STUDY MTL	NON-IRRAD STUDY MTL	IRRAD CONTROL	IRRAD STUDY MTL	NON-IRRAD STUDY MTL	IRRAD CONTROL
1)	07041	2e	0	2e	2	0	2
2)	11266	0	0	2	1	0	2
3)	12110	1	0	2	2	0	2
4)	12127	0	0	2	0	0	2
5)	15916	0	0	2	0	0	1
6)	16625	0	0	2e	0	0	2
7)	17523	1	0	2e	1	0	2
8)	17715	0	0	2	0	0	2
9)	18317	0	0	0	0	0	0
10)	18493	0	0	1	0	0	0
11)	19104	1	0	2	1	0	2

[redacted]

TKL Research, Inc. 4 Forest Avenue, Paramus, NJ 07652 (201) 587-0500 FAX (201) 587-0209

APPENDIX II

DEMOGRAPHICS

KEY:

F = Female
M = Male

C = Caucasoid
N = Negroid
H = Hispanic
M = Mongoloid
A = Asian
O = Other

STUDY#: [redacted]

TKL RESEARCH, INC.

DEMOGRAPHICS

SUBJECT #	SEX	RACE	AGE
11379	F	C	44
12883	F	C	45
14005	F	C	40
14638	F	C	35
14918	F	C	34
15426	F	C	39
15685	F	C	44
16197	F	C	36
17600	F	C	36
18537	F	C	55
18791	F	C	45

AGE DISTRIBUTION

UNDER 18	0
18 TO 25	0
26 TO 35	2
36 TO 45	8
46 TO 55	1
56 TO 65	0
OVER 65	0

TOTAL SUBJECTS 11

AGE RANGE FOR STUDY 34-55

[redacted]

STUDY#: [redacted]

TKL RESEARCH, INC.

DEMOGRAPHICS

SUBJECT #	SEX	RACE	AGE
07041	F	C	63
11266	F	C	26
12110	F	C	56
12127	F	C	57
15916	F	C	71
16625	F	C	40
17523	F	C	41
17715	F	C	35
18317	F	C	26
18493	F	C	23
19104	F	C	30

AGE DISTRIBUTION

UNDER 18	0
18 TO 25	1
26 TO 35	4
36 TO 45	2
46 TO 55	0
56 TO 65	3
OVER 65	1

TOTAL SUBJECTS 11

AGE RANGE FOR STUDY 23-71

[redacted]

HUMAN REPEATED INSULT PATCH STUDY

TKL STUDY NO. [redacted]

[redacted]

CONDUCTED FOR:

[redacted]

DATE OF REPORT:

July 29, 2004

TKL Research, Inc., 4 Forest Avenue, Paramus, NJ 07652 Tel (201) 587-0500 Fax (201) 587-0878 Email: info@tklresearch.com

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APPENDICES

SIGNATURES

Kathleen Georgeian
Kathleen Georgeian, Clinical Research Coordinator and Manager, Dermatologic Safety Testing

7/28/04
Date

Jonathan S. Dosik, MD
Principal Investigator

7/29/04
Date

STATEMENT OF QUALITY ASSURANCE

This report has been reviewed by the TKL Research, Inc. (TKL) Corporate Quality Assurance Department and the report accurately reflects the raw data for this study.

Clinical research studies are performed by TKL in accordance with all applicable federal regulations and proposed guidelines for Good Clinical Practices, which include:

21 CFR Part 312,	Investigational New Drug Application
21 CFR Part 50,	Protection of Human Subjects
21 CFR Part 56,	Institutional Review Boards

Henry Brown
Quality Assurance

7/29/04
Date

TITLE OF STUDY

Human Repeated Insult Patch Study

SPONSOR

[redacted]

STUDY MATERIAL

[redacted] Foundation Topcoat with 0.102% isopropyl titanium triisostearate.

DATE STUDY INITIATED

March 8, 2004

DATE STUDY COMPLETED

April 15, 2004

DATE OF REPORT

July 29, 2004

INVESTIGATIVE PERSONNEL

Jonathan S. Dosik, MD
Principal Investigator

Hillary Baldwin, MD
Consulting Dermatologist

Kathleen Georgeian
Clinical Research Coordinator
and Manager, Dermatologic Safety Testing

Tina Kelly
Assistant Manager, Dermatologic Safety Testing

Joanne Mruczek, RN
Senior Clinical Assistant

CLINICAL SITE

TKL RESEARCH, INC.
578 Driggs Avenue
Brooklyn, NY 11211

SUMMARY

One study material, [redacted], was evaluated neat to determine its ability to sensitize the skin of normal volunteer subjects using an occlusive repeated insult patch study. One hundred one subjects completed the study. The dermatologist was present at challenge.

Under the conditions employed in this study, there was no evidence of sensitization to [redacted] a foundation topcoat with 0.102% isopropyl titanium triisostearate.

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated 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.

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;

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 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 informed consent document in compliance with FDA regulations (21 CFR Part 50) was obtained from each subject prior to entering the study. The signed informed consent document is maintained in the study file. In addition, the subject was provided with a copy of the informed consent document (see Appendix IV).

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 consecutive 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. 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*.

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

Following the ninth 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).

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). 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 during challenge. Only completed cases were used to assess sensitization.

3.2.2 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

3.2.3 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] Foundation Topcoat with 0.102% isopropyl titanium triisostearate.
Amount Applied : 0.2 mL
Special Instructions : Applied to patch no longer then 15 minutes prior to application.

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. 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. All information regarding the receipt, storage, and disposition of the study material was also recorded on a Clinical Material Record form (see Appendix III), which is incorporated in this study report. All study material is kept in a locked product storage room accessible to clinical staff members only.

4.3 APPLICATION OF STUDY MATERIAL

Study material was applied to the patch as instructed. The patch was applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

4.4 DESCRIPTION OF PATCH CONDITIONS

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

Material evaluated under semi-occlusive patch conditions was applied to a 2-cm x 2-cm Webril pad. The pad was 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. Our preferred rechallenge procedure involves the application of the product to naïve 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 PROTOCOL

See Protocol - Appendix V.

7.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) are designed to identify each subject by subject number and initials, and to record demographics, examination results, adverse events, 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 is maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location which provides 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.

8.0 RESULTS AND DISCUSSION

One hundred seven subjects between the ages of 18 and 70 were enrolled and 101 subjects 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:		107
Number discontinued:		6
Lost to follow-up:	1	
Voluntary withdrawal:	4	
Adverse event:	1	
Number completed:		101

Source: Table 1, Appendix I

One serious non-product-related adverse event occurred. See Data Listing 4, Appendix II.

The dermatologist was present at the 72-hour challenge reading.

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

9.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to [redacted] foundation topcoat with 0.102% isopropyl titanium triisostearate.

10.0 REFERENCES

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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.

[redacted]

APPENDIX I

SUMMARY TABLES

TKL STUDY NO. [redacted]

TABLE 1: SUMMARY OF SUBJECT ENROLLMENT AND DISPOSITION

	N	(%)
SUBJECTS ENROLLED	107	
SUBJECTS COMPLETED INDUCTION PHASE	102	(95.3)
SUBJECTS COMPLETED ALL PHASES	101	(94.4)
TOTAL SUBJECTS DISCONTINUED	6	(5.6)
LOST TO FOLLOW-UP	1	(0.9)
VOLUNTARY WITHDRAWAL	4	(3.7)
ADVERSE EVENTS	1	(0.9)

NOTE: ALL PERCENTAGES ARE RELATIVE TO TOTAL SUBJECTS ENROLLED

SEE DATA LISTING 1 FOR FURTHER DETAIL

PROGRAM: DISPSMY.SAS/USES: FINAL/26APR04:11:12:33

TKL STUDY NO. [redacted]
TABLE 2: SUMMARY OF SUBJECT DEMOGRAPHICS
ALL ENROLLED SUBJECTS

AGE	
N (%) 18 TO 44	41 (38.3)
N (%) 45 TO 64	51 (47.7)
N (%) 65 AND UP	15 (14.0)
MEAN (SD)	49.0 (12.9)
MEDIAN	49.7
RANGE	18.8 TO 70.5
GENDER	
N (%) MALE	26 (24.3)
N (%) FEMALE	81 (75.7)
RACE	
N (%) CAUCASIAN	4 (3.7)
N (%) HISPANIC	103 (96.3)

SEE DATA LISTING 2 FOR FURTHER DETAIL

PROGRAM: DEMOSMY.SAS/USES: DEMOGS/26APR04:11:12:34

[redacted]

TKL STUDY NO. [redacted]

TABLE 3: SUMMARY OF DERMATOLOGIC RESPONSE GRADES
NUMBER OF SUBJECTS BY PRODUCT

PRODUCT= [redacted]

	INDUCTION READING									MAKE-	CHALLENGE PHASE		
RESPONSE	1	2	3	4	5	6	7	8	9	UP	48HR	72HR	96HR(*)
-	106	103	102	101	100	101	101	101	102	13	101	101	
TOTAL EVALUABLE	106	103	102	101	100	101	101	101	102	13	101	101	
NUMBER ABSENT	0	1	2	3	4	1	1	1	0		0	0	
NUMBER DISCONTINUED	1	3	3	3	3	5	5	5	5		6	6	

MAXIMUM ELICITED RESPONSE DURING INDUCTION
ALL SUBJECTS COMPLETING INDUCTION (N=102)

RESPONSE	N(%) SUBJECTS
-	102 (100.0%)

(*) WHEN REQUIRED

KEY TO SYMBOLS:
- = 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
D = DAMAGE TO EPIDERMIS: OOZING, CRUSTING AND/OR SUPERFICIAL EROSIONS
P = PAPULAR RESPONSE >50%

PROGRAM: SUMMARY.SAS/USES: RESPONSE, PRODLIST, FINAL/26APR04:11:12:38

APPENDIX II

DATA LISTINGS

TKL STUDY NO. [redacted]
DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

SUBJECT NO.	STUDY DATES SCREENED	1ST APPLIC	CHALL APPLIC	ENDED	LAST READING #	COMPLETION STATUS	DAYS ON STUDY
1	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
2	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
3	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
4	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
5	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
6	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
7	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
8	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
9	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
10	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
11	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
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14	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
15	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
16	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
17	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
18	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
19	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
20	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
21	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
22	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
23	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
24	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
25	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
26	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
27	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
28	03/08/04	03/08/04		03/24/04	I5	S	17
29	03/08/04	03/08/04		03/24/04	I5	L	17
30	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
31	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
32	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
33	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
34	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
35	03/08/04	03/08/04		03/15/04	I1	S	8
36	03/08/04	03/08/04		03/15/04	I1	S	8
37	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
38	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
39	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39

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)

PROGRAM: DISPLIST.SAS/USES: DEMOGS, RESPONSE, FINAL/26APR04:11:12:25

TKL STUDY NO. [redacted]
DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

SUBJECT NO.	STUDY DATES SCREENED	1ST APPLIC	CHALL APPLIC	ENDED	LAST READING #	COMPLETION STATUS	DAYS ON STUDY
40	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
41	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
42	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
43	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
44	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
45	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
46	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
47	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
48	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
49	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
50	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
51	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
52	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
53	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
54	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
55	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
56	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
57	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
58	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
59	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
60	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
61	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
62	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
63	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
64	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
65	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
66	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
67	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
68	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
69	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
70	03/08/04	03/08/04		04/12/04	I9	AE	36
71	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
72	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
73	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
74	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
75	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
76	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
77	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
78	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39

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)

PROGRAM: DISPLIST.SAS/USES: DEMOGS, RESPONSE, FINAL/26APR04:11:12:25

TKL STUDY NO. [redacted]
DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

SUBJECT NO.	STUDY DATES: SCREENED	1ST APPLIC	CHALL APPLIC	ENDED	LAST READING #	COMPLETION STATUS	DAYS ON STUDY
79	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
80	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
81	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
82	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
83	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
84	03/08/04	03/08/04		03/10/04	I0	S	3
85	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
86	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
87	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
88	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
89	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
90	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
91	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
92	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
93	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
94	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
95	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
96	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
97	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
98	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
99	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
100	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
101	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
102	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
103	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
104	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
105	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
106	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39
107	03/08/04	03/08/04	04/12/04	04/15/04	C2	C	39

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)

PROGRAM: DISPLIST.SAS/USES: DEMOGS, RESPONSE, FINAL/26APR04:11:12:25

TKL STUDY NO. [redacted]
DATA LISTING 2: SUBJECT DEMOGRAPHICS

SUBJECT NO.	AGE	GENDER	RACE
1	45.6	FEMALE	HISPANIC
2	59.9	MALE	HISPANIC
3	58.7	MALE	HISPANIC
4	62.3	FEMALE	HISPANIC
5	55.8	FEMALE	HISPANIC
6	38.2	MALE	HISPANIC
7	61.7	FEMALE	HISPANIC
8	65.8	FEMALE	HISPANIC
9	57.2	FEMALE	HISPANIC
10	42.1	FEMALE	HISPANIC
11	44.6	MALE	HISPANIC
12	37.9	FEMALE	HISPANIC
13	54.1	FEMALE	CAUCASIAN
14	32.8	FEMALE	HISPANIC
15	28.8	FEMALE	HISPANIC
16	52.0	FEMALE	HISPANIC
17	35.5	FEMALE	HISPANIC
18	38.6	FEMALE	HISPANIC
19	63.8	FEMALE	HISPANIC
20	45.0	MALE	HISPANIC
21	44.6	FEMALE	HISPANIC
22	36.4	FEMALE	HISPANIC
23	53.0	FEMALE	HISPANIC
24	39.6	FEMALE	HISPANIC
25	42.2	MALE	HISPANIC
26	66.6	FEMALE	HISPANIC
27	48.2	MALE	HISPANIC
28	46.5	FEMALE	HISPANIC
29	26.0	FEMALE	HISPANIC
30	59.9	FEMALE	HISPANIC
31	32.8	FEMALE	HISPANIC
32	57.0	MALE	HISPANIC
33	40.7	FEMALE	HISPANIC
34	48.8	FEMALE	HISPANIC
35	30.5	FEMALE	HISPANIC
36	69.1	FEMALE	HISPANIC
37	27.6	FEMALE	HISPANIC
38	58.6	MALE	HISPANIC
39	56.2	FEMALE	HISPANIC
40	54.4	FEMALE	HISPANIC

PROGRAM: DEMOLIST.SAS/USES: DEMOGS/26APR04:11:12:25

SUBJECT NO.	AGE	GENDER	RACE
41	56.9	FEMALE	HISPANIC
42	36.9	MALE	HISPANIC
43	66.5	FEMALE	HISPANIC
44	57.0	FEMALE	HISPANIC
45	64.6	FEMALE	HISPANIC
46	69.0	FEMALE	HISPANIC
47	50.8	FEMALE	HISPANIC
48	54.2	FEMALE	HISPANIC
49	56.8	MALE	HISPANIC
50	53.0	FEMALE	HISPANIC
51	26.5	FEMALE	HISPANIC
52	36.9	FEMALE	HISPANIC
53	45.5	FEMALE	HISPANIC
54	42.4	MALE	HISPANIC
55	61.7	FEMALE	HISPANIC
56	35.4	MALE	HISPANIC
57	66.9	MALE	HISPANIC
58	67.0	FEMALE	HISPANIC
59	24.9	FEMALE	HISPANIC
60	19.9	FEMALE	HISPANIC
61	56.3	FEMALE	HISPANIC
62	69.5	FEMALE	HISPANIC
63	42.1	FEMALE	HISPANIC
64	69.7	FEMALE	HISPANIC
65	70.3	FEMALE	HISPANIC
66	49.6	FEMALE	HISPANIC
67	43.3	MALE	HISPANIC
68	70.5	FEMALE	HISPANIC
69	66.1	FEMALE	HISPANIC
70	56.3	FEMALE	HISPANIC
71	62.5	MALE	HISPANIC
72	47.0	FEMALE	CAUCASIAN
73	50.6	FEMALE	HISPANIC
74	53.0	FEMALE	HISPANIC
75	55.9	FEMALE	CAUCASIAN
76	70.5	FEMALE	HISPANIC
77	45.7	MALE	HISPANIC
78	44.3	FEMALE	HISPANIC
79	23.4	FEMALE	HISPANIC
80	52.6	FEMALE	HISPANIC

TKL STUDY NO. [redacted]
DATA LISTING 2: SUBJECT DEMOGRAPHICS

SUBJECT NO.	AGE	GENDER	RACE
81	40.0	FEMALE	HISPANIC
82	46.0	MALE	HISPANIC
83	34.3	FEMALE	HISPANIC
84	39.3	MALE	HISPANIC
85	68.8	FEMALE	HISPANIC
86	42.3	FEMALE	HISPANIC
87	49.4	FEMALE	HISPANIC
88	35.0	FEMALE	HISPANIC
89	49.8	MALE	HISPANIC
90	55.1	FEMALE	HISPANIC
91	38.7	FEMALE	HISPANIC
92	62.6	FEMALE	HISPANIC
93	49.7	FEMALE	HISPANIC
94	56.8	FEMALE	CAUCASIAN
95	50.4	MALE	HISPANIC
96	18.8	MALE	HISPANIC
97	29.7	MALE	HISPANIC
98	30.4	FEMALE	HISPANIC
99	30.1	MALE	HISPANIC
100	48.7	FEMALE	HISPANIC
101	41.6	FEMALE	HISPANIC
102	38.6	MALE	HISPANIC
103	43.1	FEMALE	HISPANIC
104	50.8	MALE	HISPANIC
105	66.2	FEMALE	HISPANIC
106	55.2	FEMALE	HISPANIC
107	59.1	FEMALE	HISPANIC

[redacted]
TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= [redacted]

SUBJECT NO.	INDUCTION READING 1	2	3	4	5	6	7	8	9	MU	CHALLENGE PHASE 48HR	72HR	96HR(*)
1	-	-	-	-	-	-	-	-	-		-	-	
2	-	-	-	-	-	-	-	-	-		-	-	
3	-	-	-	-	-	-	-	-	-		-	-	
4	-	-	-	-	-	-	-	-	-		-	-	
5	-	-	-	-	-	-	-	-	-		-	-	
6	-	-	-	-	-	-	-	-	-		-	-	
7	-	-	-	-	-	-	-	-	-		-	-	
8	-	-	-	-	-	-	-	-	-		-	-	
9	-	-	-	-	-	-	-	-	-		-	-	
10	-	-	-	-	-	-	-	-	-		-	-	
11	-	-	-	-	-	-	-	-	-		-	-	
12	-	-	-	-	-	-	-	-	-		-	-	
13	-	-	-	-	-	-	-	-	-		-	-	
14	-	-	X	-	-	-	-	-	-	-	-	-	
15	-	-	-	-	-	-	-	-	-		-	-	
16	-	-	-	-	-	-	-	-	-		-	-	
17	-	-	-	-	-	-	-	-	-		-	-	
18	-	-	-	-	-	-	-	-	-		-	-	
19	-	-	-	-	-	-	-	-	-		-	-	
20	-	-	X	-	-	-	-	-	-	-	-	-	

KEY TO SYMBOLS:

- = 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

N9G = NO NINTH GRADING NA=NOT APPLIED NP=NOT PATCHED DUE TO REACTION ACHIEVED
X = READING NOT PERFORMED DUE TO MISSED VISIT OR SUBJECT DISCONTINUATION
D = DAMAGE TO EPIDERMIS: OOZING, CRUSTING AND/OR SUPERFICIAL EROSIONS
P = PAPULAR RESPONSE >50% NR=DATA NOT RECORDED
MU = MAKE-UP READING FOR MISSED INDUCTION VISIT

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/26APR04:11:12:26

[redacted]
TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= [redacted]

SUBJECT	INDUCTION READING										CHALLENGE PHASE		
NO.	1	2	3	4	5	6	7	8	9	MU	48HR	72HR	96HR(*)
21	-	-	-	-	-	-	-	-	-		-	-	
22	-	-	-	-	-	-	-	-	-		-	-	
23	-	-	-	-	X	-	-	-	-	-	-	-	
24	-	-	-	-	-	-	-	X	-	-	-	-	
25	-	-	-	-	-	-	-	-	-		-	-	
26	-	-	-	-	-	-	-	-	-		-	-	
27	-	-	-	-	-	-	-	-	-		-	-	
28	-	-	-	-	-	X	X	X	X		X	X	
29	-	-	-	-	-	X	X	X	X		X	X	
30	-	-	-	-	-	-	-	-	-		-	-	
31	-	-	-	-	-	-	-	-	-		-	-	
32	-	-	-	-	-	-	-	-	-		-	-	
33	-	-	-	-	-	-	-	-	-		-	-	
34	-	-	-	-	-	-	-	-	-		-	-	
35	-	X	X	X	X	X	X	X	X		X	X	
36	-	X	X	X	X	X	X	X	X		X	X	
37	-	-	-	-	-	-	-	-	-		-	-	
38	-	-	-	-	-	-	-	-	-		-	-	
39	-	-	-	-	X	-	-	-	-	-	-	-	
40	-	-	-	-	-	-	-	-	-		-	-	
41	-	-	-	-	-	-	-	-	-		-	-	
42	-	-	-	-	-	-	-	-	-		-	-	
43	-	-	-	-	-	-	-	-	-		-	-	
44	-	-	-	-	-	-	-	-	-		-	-	
45	-	-	-	-	-	-	-	-	-		-	-	
46	-	-	-	-	-	-	-	-	-		-	-	
47	-	-	-	-	-	-	-	-	-		-	-	
48	-	-	-	X	-	-	-	-	-	-	-	-	
49	-	-	-	-	-	-	-	-	-		-	-	
50	-	-	-	-	-	-	-	-	-		-	-	
51	-	-	-	-	-	-	-	-	-		-	-	
52	-	-	-	-	-	-	-	-	-		-	-	

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/26APR04:11:12:26

[redacted]
TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= [redacted]

SUBJECT	INDUCTION READING										CHALLENGE PHASE	
NO.	1	2	3	4	5	6	7	8	9	MU	48HR	72HR 96HR(*)
53	-	-	-	-	-	-	-	-	-		-	-
54	-	-	-	-	-	-	-	-	-		-	-
55	-	-	-	-	-	-	-	-	-		-	-
56	-	-	-	-	-	-	-	-	-		-	-
57	-	-	-	-	-	-	-	-	-		-	-
58	-	-	-	-	-	-	-	-	-		-	-
59	-	-	-	-	-	-	-	-	-		-	-
60	-	X	-	-	-	-	-	-	-	-	-	-
61	-	-	-	-	-	-	-	-	-		-	-
62	-	-	-	-	-	-	-	-	-		-	-
63	-	-	-	-	-	-	-	-	-		-	-
64	-	-	-	-	-	-	-	-	-		-	-
65	-	-	-	-	-	-	-	-	-		-	-
66	-	-	-	-	-	-	-	-	-		-	-
67	-	-	-	-	-	-	-	-	-		-	-
68	-	-	-	-	-	-	-	-	-		-	-
69	-	-	-	-	-	-	-	-	-		-	-
70	-	-	-	-	-	-	-	-	-		X	X
71	-	-	-	-	-	-	-	-	-		-	-
72	-	-	-	-	-	-	-	-	-		-	-
73	-	-	-	-	-	-	X	-	-	-	-	-
74	-	-	-	-	-	-	-	-	-		-	-
75	-	-	-	-	-	-	-	-	-		-	-
76	-	-	-	-	-	-	-	-	-		-	-
77	-	-	-	-	-	-	-	-	-		-	-
78	-	-	-	-	-	-	-	-	-		-	-
79	-	-	-	-	-	-	-	-	-		-	-
80	-	-	-	-	-	-	-	-	-		-	-
81	-	-	-	-	-	-	-	-	-		-	-
82	-	-	-	-	-	X	-	-	-	-	-	-
83	-	-	-	-	-	-	-	-	-		-	-
84	X	X	X	X	X	X	X	X	X		X	X

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/26APR04:11:12:26

[redacted]
TKL STUDY NO. [redacted]
DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

PRODUCT= [redacted]

SUBJECT	INDUCTION READING										CHALLENGE PHASE		
NO.	1	2	3	4	5	6	7	8	9	MU	48HR	72HR	96HR(*)
85	-	-	-	X	-	-	-	-	-	-	-	-	
86	-	-	-	X	-	-	-	-	-	-	-	-	
87	-	-	-	-	-	-	-	-	-		-	-	
88	-	-	-	-	-	-	-	-	-		-	-	
89	-	-	-	-	-	-	-	-	-		-	-	
90	-	-	-	-	X	-	-	-	-	-	-	-	
91	-	-	-	-	-	-	-	-	-		-	-	
92	-	-	-	-	-	-	-	-	-		-	-	
93	-	-	-	-	X	-	-	-	-	-	-	-	
94	-	-	-	-	-	-	-	-	-		-	-	
95	-	-	-	-	-	-	-	-	-		-	-	
96	-	-	-	-	-	-	-	-	-		-	-	
97	-	-	-	-	-	-	-	-	-		-	-	
98	-	-	-	-	-	-	-	-	-		-	-	
99	-	-	-	-	-	-	-	-	-		-	-	
100	-	-	-	-	-	-	-	-	-		-	-	
101	-	-	-	-	-	-	-	-	-		-	-	
102	-	-	-	-	-	-	-	-	-		-	-	
103	-	-	-	-	-	-	-	-	-		-	-	
104	-	-	-	-	-	-	-	-	-		-	-	
105	-	-	-	-	-	-	-	-	-		-	-	
106	-	-	-	-	-	-	-	-	-		-	-	
107	-	-	-	-	-	-	-	-	-		-	-	

(*) WHEN REQUIRED

PROGRAM: DETAIL.SAS/USES: RESPONSE, PRODLIST/26APR04:11:12:26

TKL STUDY NO. [redacted]
DATA LISTING 4: ADVERSE EVENTS

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SUBJECT NO. 70

ADVERSE EVENT: [redacted]

DATE OF ONSET: 04/06
DATE OF RESOLUTION: 04/06
FREQUENCY: SINGLE EPISODE
SEVERITY: [redacted]
DURATION: 5 SECONDS
OUTCOME: [redacted]
REL. TO STUDY PRODUCT: UNRELATED
ACTION TAKEN/STUDY PRODUCT: DISCONTINUED
ACTION TAKEN/TREATMENT?: NO
SERIOUS? [redacted]

COMMENT: [redacted]

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PROGRAM: AE.SAS/USES: AE, COMMENTS/26APR04:11:12:29

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

DATE: April 2, 2018

SUBJECT: Scientific Literature Review: Safety Assessment of Organo-Titanium Ingredients as Used in Cosmetics (release date: March 13, 2018)

The Council has no suppliers for the following ingredients included in the report on organo-titanium ingredients:

Titanium Citrate
Titanium Salicylate

The Council respectfully submits the following comments on the Scientific Literature Review: Safety Assessment of Organo-Titanium Ingredients as Used in Cosmetics.

Introduction, Summary - As only one ingredient in this assessment has reported uses in cosmetics, please state that the reported function for Isopropyl Titanium Triisostearate is surface modifier, and make it clear that the other functions listed do not apply to all of the ingredients in the report, e.g., functions reported for at least one of the other ingredients in the report include colorants, humectants....

Cosmetic Use - As there is more than one ingredient in this report, "this ingredient" needs to be corrected to "these ingredients" in the first paragraph of the Cosmetic Use section.

It would be helpful to state that although colorants is listed as a function for Titanium Citrate, it is not an approved colorant in the United States or Europe.

ADME, Titanium Citrate - Although Titanium Citrate may have been used to dose the everted sac model, the title (reference 2) suggests that they were studying the uptake of titanium from Titanium Citrate, not Titanium Citrate itself. Some indication of the absorption rate and time-frame of the study should be stated.

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