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Titanium Complexes as Used in Cosmetics

Wilbur Johnson Jr.*, Wilma F. Bergfeld, Donald V. Belsito**, Ronald A. Hill***, Curtis D. Klaassen**, Daniel C. Liebler***, James G. Marks Jr.***, Ronald C. Shank***, Thomas J. Slaga***, Paul W. Snyder**, Monice Fiume†, and Bart Heldreth††**

Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 5 titanium complexes as used in cosmetic products; these ingredients have the following reported functions in cosmetics: surface modifier (Isopropyl Titanium Triisostearate); colorant; humectant (Titanium Citrate); binder (Titanium Ethoxide); film former; opacifying agent (Titanium Isostearates); and preservative (Titanium Salicylate). The Panel reviewed relevant data relating to the safety of these ingredients in cosmetic formulations and issued the following separate conclusions. Isopropyl Titanium Triisostearate is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when used as a surface modifier. The data are insufficient to determine the safety of Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, and Titanium Salicylate.

Keywords

Isopropyl Titanium Triisostearate, Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, Titanium Salicylate, Cosmetic Ingredient Review, Expert Panel for Cosmetic Ingredient Safety, Safety, Cosmetics

Introduction

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

Isopropyl Titanium Triisostearate
Titanium Citrate
Titanium Ethoxide
Titanium Isostearates
Titanium Salicylate

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

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated.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

Chemistry

Definition and General Characterization

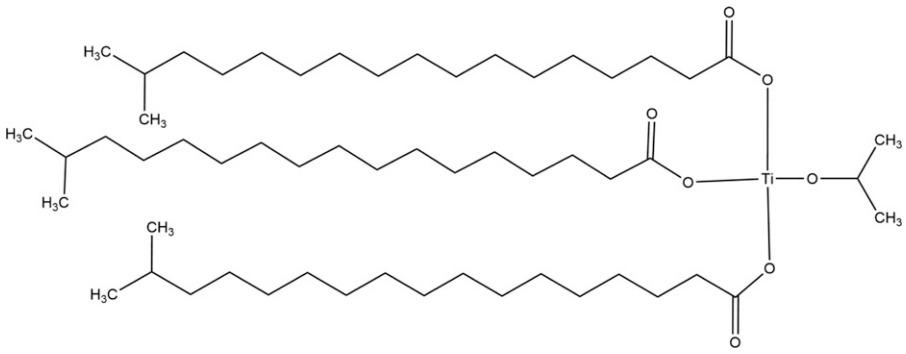
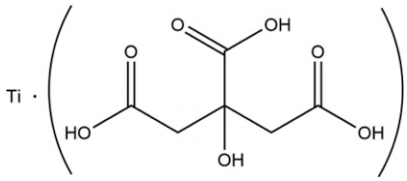
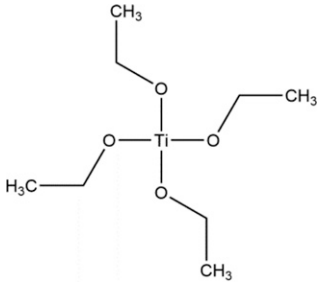
The definitions, structures, and functions in cosmetics of these ingredients are presented in Table 1.[1] The ingredients in this group are tetravalent complexes of titanium (Figure 1).

When the oxidation state of titanium is 4 or greater ($n > 4$ in Figure 1) the titanium-bonding character is coordinate. The ingredients in this report are presumed to all comprise

*Cosmetic Ingredient Review Former Scientific Analyst/Writer
**Expert Panel for Cosmetic Ingredient Safety Member
***Expert Panel for Cosmetic Ingredient Safety Former Member
†Cosmetic Ingredient Review Senior Director
††Cosmetic Ingredient Review Executive Director

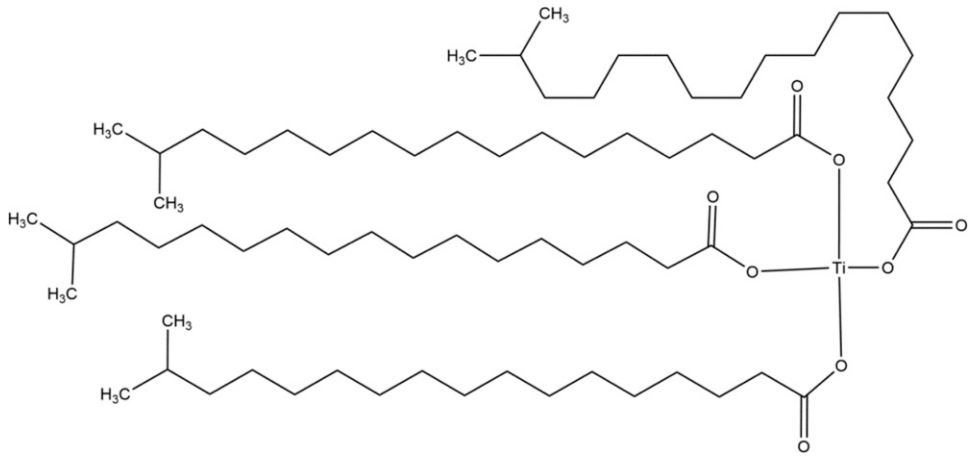
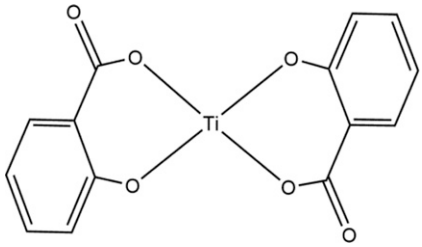
Corresponding Author:
Bart Heldreth, Executive Director, Cosmetic Ingredient Review, 555 13th Street, NW, Suite 300W, Washington, DC 20004, USA.
Email: cirinfo@cir-safety.org

Table 1. Definitions, Idealized Structures, and Functions of the Ingredients in This Safety Assessment.[1; CIR Staff]

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

(continued)

Table 1. (continued)

Ingredient CAS No.	Definition and Structures	Function(s)
Titanium Isostearates	Titanium Isostearates is the product formed by the reaction of titanium tetraethoxide and isostearic acid. 	Film Formers; Opacifying Agents
Titanium Salicylate	Titanium Salicylate is the titanium salt of salicylic acid. 	Preservatives

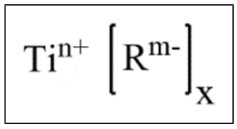


Figure 1. Generic formula of titanium complexes.

complexes of titanium wherein the oxidation state is 4^{+}. Accordingly, structures for these chemicals have been drawn with solid lines indicating oxygen-titanium bonds for the sake of convenience (Figure 2).

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

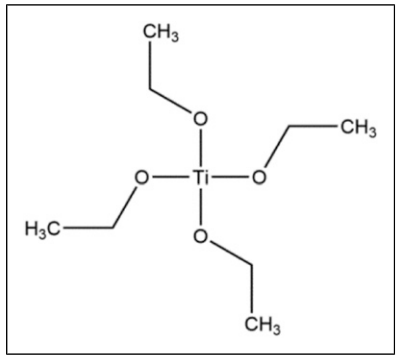


Figure 2. Titanium Ethoxide.

Isopropyl Titanium Triisostearate in the product formulation would be considered an impurity.

No data have been submitted to suggest that Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, or Titanium

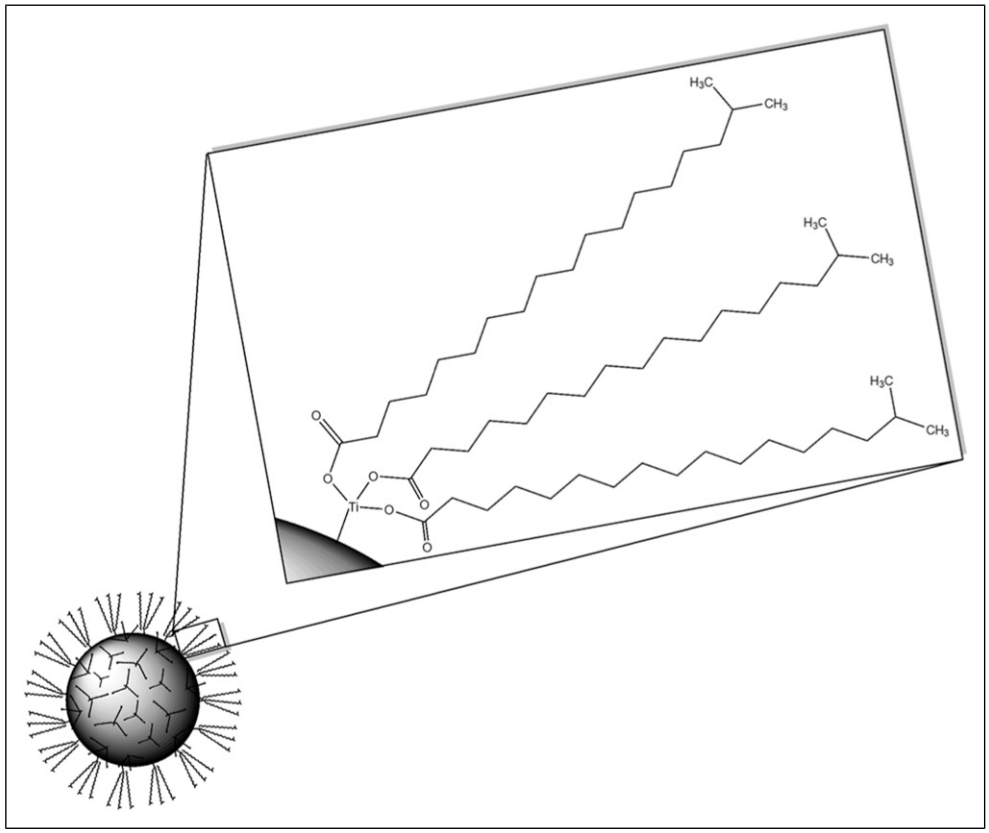


Figure 3. Idealized view of a pigment particle, surface modified by reaction with Isopropyl Titanium Triisostearate (depicted isostearyl chains are one example of an "iso").

Salicylate are used in cosmetic formulations to modify pigment surfaces in this way. Accordingly, the available information suggests that these 4 ingredients are discrete, unreacted complexes (e.g., Figure 2).

Chemical Properties

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

Method of Manufacture

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

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

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

Composition and Impurities

Isopropyl Titanium Triisostearate. A chemical supplier has reported that Isopropyl Titanium Triisostearate consists of 98%

Table 2. Chemical and Physical Properties of Titanium Complexes Ingredients.

Property	Value/Results	Reference
Isopropyl Titanium Triisostearate		
Form	Reddish liquid	4
Odor	Waxy fatty acid	4
Molecular weight (Da)	961.415 (for the unreacted, discrete complex; not as a coated colorant particle)	33
pH (solvent not stated)	5-6	4
Solubility	Insoluble in water; soluble in <5% xylene	4
Viscosity (cps @ 77°F)	125	4
Evaporation rate (relative to n-butyl acetate) slower	Slower	4
Boiling point (°C)	149	4
Titanium citrate		
Solubility	Soluble in water	2
Dissociation	Dissociation of free citrate increased with rise in pH (i.e., with increased alkalinity).	2
Titanium ethoxide		
Form	White solid	34
	Light-yellow liquid	3
Odor	Similar to alcohol	34
Molecular weight (Da)	228.11	
Melting point (°C)	54	34
Flash point (°C)	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 $t_{1/2}$ (min)	≤ 3 to <120	3
Titanium salicylate		
Molecular weight (Da)	320.08	35

Isopropyl Titanium Triisostearate and <2% isopropyl alcohol.[4]

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

Use

Cosmetic

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

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

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

Cosmetic products containing Isopropyl Titanium Triisostearate may be applied to the skin or, incidentally, may

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

	Isopropyl Titanium Triisostearate	
	# of Uses	Conc. (%)
Totals/conc. range	513	0.00002–1.4
Duration of use		
Leave-on	*506*	*0.00002–1.4*
Rinse off	7	*0.18–0.3*
Diluted for (bath) use	*NR*	*NR*
Exposure type		
Eye area	99	0.00002–1.4
Incidental ingestion	253	0.08–0.42
Incidental inhalation—sprays	5[a];3[b]	NR
Incidental inhalation—powders	21;3[b]	0.25–0.75
Dermal contact	229	0.0002–1.4
Deodorant (underarm)	NR	NR
Hair—non-coloring	NR	NR
Hair—coloring	NR	NR
Nail	7	0.18
Mucous membrane	257	0.08–0.42
Baby products	NR	NR

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.
NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.
[a]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.
[b]Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

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

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

Non-Cosmetic

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

Toxicokinetic Studies

Dermal Penetration

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

Absorption, Distribution, Metabolism, and Excretion

In Vitro

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

Human

OralTitanium Salicylate

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

Toxicological Studies

Acute Toxicity Studies

Dermal

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

Oral

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

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

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

Parenteral

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

Short-Term Toxicity Studies

Oral

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

Subchronic Toxicity Studies

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

Chronic Toxicity Studies

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

Developmental and Reproductive Toxicity Studies

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

Genotoxicity Studies

In Vitro

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

Carcinogenicity Studies

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

Anti-Tumorigenicity Study

Titanium Citrate

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

Other Relevant Studies

Cytotoxicity

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

intense hemolysis that affected the great majority of the erythrocytes. Numerous erythrocytes were ruptured, resulting in empty and retracted membranes (i.e., erythrocyte ghosts).

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

Dermal Irritation and Sensitization Studies

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

Irritation

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

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

Sensitization

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

Photosensitization/Phototoxicity

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

Ocular Irritation Studies

In Vitro

Isopropyl Titanium Triisostearate. The ocular irritation potential of 2 foundation topcoats containing 0.102% Isopropyl Titanium Triisostearate (used as a surface modifier) was evaluated using the EpiOcular™ human cell construct (reconstructed human cornea-like epithelium).[31] Toxicity was measured by the reduction of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium

Table 4. Skin Irritation and Sensitization Studies on Titanium Complexes.

Test Substance	Animals/ Subjects/Cells	Test Protocol	Results
Irritation (Animal)			
Isopropyl Titanium Triisostearate (98% Isopropryl Titanium Triisostearate and <2% isopropyl alcohol; not used as a surface modifier)	New Zealand white rabbits (number not stated)	Test substance (dose/cm^2 not stated) administered under semi-occlusive wrap for 4 h. Scores for erythema recorded at 4 h, 24 h, 48 h, and 72 h after patch removal	Primary dermal irritation scores: Erythema (0.3), edema (0), and overall score (0.3). Test substance was non-corrosive.[17]
Black iron oxide with 2% Isopropyl Titanium Triisostearate (colorant particles surface modified with Isopropyl Titanium Triisostearate)	Six New Zealand white rabbits	Test substance (0.5 g, moistened with saline) applied for 24 h, under occlusive patch (5 cm^2), to intact and abraded sites on opposite sides of vertebral column. Patch was secured with hypoallergenic cloth tape. Reactions scored at 24 h and 72 h post-application. Mean irritation scores averaged to determine the PII (≥5 = skin irritant)	PII = 0. Test substance was non-irritating to abraded and intact skin.[22]
Titanium salicylates (concentration not stated). Chemical structures not provided. Whether or not titanium salicylates is inclusive of discrete chemical (Titanium Salicylate, cosmetic ingredient) is unknown	Rabbits (number and strain not stated)	Protocol details not stated.	Test substance did not cause skin irritation.[16]
Irritation (Human)			
Concealer containing 0.4% Isopropyl Titanium Triisostearate (colorant particles surface modified with Isopropyl Titanium Triisostearate, i.e. use as a surface modifier)	23 subjects	SIOPT. Test substance (dose/cm^2 not stated)	Test substance did not cause skin irritation.[23]
Sensitization (Human)			
Foundation containing 0.348% Isopropyl Titanium Triisostearate (used as a surface modifier)	108 male and female subjects	HRIPT. During induction, occlusive patch containing product applied to upper back (patch dimensions and amount applied not stated; dose per cm^2 unknown). Induction phase (9 applications): Patches applied for 24 h to the same site on Mondays, Wednesdays and Fridays. Sites evaluated at 24 h after patch removal on Tuesdays and Thursdays, and at 48 h after patch removal on Saturdays. After non-treatment period (~2 weeks), challenge patch applied for 24 h to new site on back. Sites evaluated at 24 h, 48 h, and 72 h after patch removal.	No evidence of skin irritation or sensitization in any of the subjects tested.[27]

(continued)

Table 4. (continued)

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

(continued)

Table 4. (continued)

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

bromide (MTT) to a blue formazan precipitate. The duration of exposure that resulted in a 50% decrease in MTT conversion in treated human cell constructs relative to control cultures (t_{50}) was determined (t_{50} > 24 h = non-irritating). Each foundation topcoat was tested alone and as a 50:50 mixture of the two. Human cell constructs were exposed to the test materials for up to 24 h. When the 2 foundation topcoats were tested alone, t_{50} values of 15.4 h and >24 h were reported. The 50:50 mixture yielded a t_{50} of 15.2 h. The positive control (0.3% Triton®-X-100) yielded a t_{50} of 23.4 min. A conclusion describing the ocular irritation potential of the foundation topcoats was not stated. However, a t_{50} of <24 h would be indicative of some degree of ocular irritation.

Animal

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

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

If any of the test substance remained in the eye at 24 h, the eye was rinsed with water after the 24-h reading. The test substance was classified as a minimal ocular irritant.

Other Clinical Reports

Retrospective Study

Titanium Citrate. A retrospective chart review was conducted on 458 patients who underwent patch testing with Titanium Citrate and other titanium salts, over a 10-year period.[32] The patch testing of titanium salts was performed at a dermatology clinic in the Netherlands, using van der Bend chambers that were applied to the back for 48 h. Reactions were scored on days 2, 3, and 7 according to International Contact Dermatitis Research Group (ICDRG)/European Society of Contact Dermatitis (ESCD) criteria. Reactions identified as +, ++, or +++ were classified as positive, whereas doubtful reactions (?+) were not. At least one positive reaction was observed in 26 (5.7%) of the 458 patients patch tested. Fifteen (57.7%) of these 26 patients had a proven titanium-containing implant or reconstructive material. Also, most of the titanium-positive patients had local symptoms, that is, pain, erythema, dermatitis, pruritus, impaired wound healing, and swelling. For 16 (61.5%) of the 26 positive patients, a positive result was determined (due to confounding factors such as the multifactorial background of complaints following implantation and potential sensitization resulting from other components used in implants, the authors experienced difficulties in determining whether a positive reaction to titanium was putatively responsible for the clinical complaints (i.e., complete relevance)). Overall, the percentage of positive reactions induced by each titanium salt was reported as follows: titanium (IV) oxalate hydrate (7.9%; 17 of 216 patients tested), titanium lactate (4.4%; 2 of 45 patients tested), titanium (IV) isopropoxide (2.9%; 8 of 272 patients tested), Titanium Citrate (2.2%; 1 of 45 patients tested), and titanium dioxide (0.9%; 3 of 329 patients tested).

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

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

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

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

Summary

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

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

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

Following the oral administration of titanium salicylates (~10 mg) to one human subject, titanium was detected in the feces and urine, with evidence that salicylate remained

attached to titanium in the urine. Though the definition of titanium salicylates is not provided in this study, it is possible that these data may be useful in evaluating the toxicokinetics of Titanium Salicylate.

There were no signs of gross toxicity or remarkable pathology in New Zealand White rabbits (number not stated), after application of 98% Isopropyl Titanium Triisostearate (in isopropanol) under a semi-occlusive wrap for 4 h. Whether or not this test article is being used as a surface modifier was not stated.

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

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

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

In a skin irritation study involving New Zealand White rabbits (number not stated), 98% Isopropyl Titanium Triisostearate (in isopropanol) was classified as non-corrosive. Black iron oxide with 2% Isopropyl Titanium Triisostearate did not induce skin irritation (intact or abraded skin) in a study involving 6 New Zealand white rabbits. The topical application of titanium salicylates (concentration not stated) to the skin of rabbits did not cause skin irritation. In an SIOPT, skin irritation was not observed in any of the 23 subjects patch-tested with a concealer containing 0.4% Isopropyl Titanium Triisostearate (used as a surface modifier).

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

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

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

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

The hemolytic activity of Titanium Citrate in human erythrocytes in vitro has been observed at concentrations

ranging from 0.0025 to 0.8 mM. At a concentration of 0.8 mM, numerous erythrocytes ruptured, resulting in empty and retracted membranes (i.e., erythrocyte ghosts).

Discussion

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

Available data on the method of manufacture demonstrate that, as a surface modifier in cosmetics, Isopropyl Titanium Triisostearate is covalently bound to a pigment (e.g., black iron oxide). Thus, the presence of any residual or unreacted Isopropyl Titanium Triisostearate in the product formulation would be considered an impurity. The Panel noted that if data are provided that indicate the presence of significant levels of residual unbound Isopropyl Titanium Triisostearate when used as a surface modifier, 28-day dermal toxicity data and genotoxicity data would then be needed to evaluate the safety of this ingredient. The same would apply to any other identified use(s) of this ingredient that would yield free Isopropyl Titanium Triisostearate in the product formulation. No data have been submitted to suggest that Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, or Titanium Salicylate are used in cosmetic formulations to modify pigment surfaces in this way. Therefore, the available information suggests that these four ingredients are discrete, unreacted complexes.

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

(i) Maximum use concentrations
(ii) Methods of manufacture
(iii) Impurities
(iv) 28-day dermal toxicity data
    1. Depending on the results of these studies, various systemic toxicity data may also be needed
(v) Skin irritation and sensitization data at cosmetic use concentrations, except for Titanium Citrate

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

With the exceptions of HRIPT data on an experimental product containing 1.4% Isopropyl Titanium Triisostearate, phototoxicity data (humans) on a pressed powder containing 0.0004% Isopropyl Titanium Triisostearate, and acute oral and dermal toxicity, genotoxicity, and skin and ocular irritation data on Isopropyl Titanium Triisostearate (98% Isopropyl Titanium Triisostearate and <2% isopropyl alcohol); the ingredient Isopropyl Titanium Triisostearate was used as a surface modifier in all of the studies that were provided by the Council. Confirmation that the Council's use concentration data on Isopropyl Titanium Triisostearate relate to the use this ingredient as a surface modifier was received, as were additional HRIPT data on Isopropyl Titanium Triisostearate (used as a surface modifier). Information on whether or not the remaining ingredients in this safety assessment function as surface modifiers also has not been provided.

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

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that Isopropyl Titanium Triisostearate is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when used as a surface modifier. The Panel also concluded that the data are insufficient to determine the safety of the following 4 ingredients: Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, and Titanium Salicylate. These ingredients are not reported to be in use.

Author's Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 555 13th Street, NW, Suite 300W, Washington, DC 20004, USA.

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References

1. Nikitakis J, Lange B. International Cosmetic Ingredient Dictionary and Handbook Online Version (wINCI). Washington, DC. https://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Last Updated 2018. Accessed April 27, 2018.
2. Deng Y, Jiang Y, Hong Q, Zhou ZH. Speciation of water-soluble titanium citrate: synthesis, structural, spectroscopic properties and biological relevance. *Polyhedron*. 2007;26(8):1561-1569.
3. European Chemicals Agency (ECHA). Registration, Evaluation, and Authorization of Chemicals (REACH) Dossier. *Titanium (4+) ethanolate*. https://echa.europa.eu/registration-dossier/-/registered-dossier/13707/4/2. Last Updated 2018. Accessed January 25, 2018.
4. Kenrich Petrochemicals, Inc. Summary information. Isopropyl Titanium Triisostearate. Unpublished data submitted by the Personal Care Products Council on 5-15-2018; 2018. p. 1.
5. Kobo Products, Inc. Isopropyl titanium triisostearate surface treatment. Unpublished data submitted by the Personal Care Products Council on 7-9-2018; 2018. pp. 1-3.
6. Aarabi MH, Moshtaghie AA, Mirhashemi M. Comparative in vitro study of the intestinal absorption of titanium and iron in rats. *Pak J Biol Sci*. 2011;14(20):945-949.
7. SGS. Test report (metal analysis of TIPT (titanium compound used in the manufacture of isopropyl titanium triisostearate)). Unpublished data submitted by the Personal Care Products Council on 5-15-2018; 2016. pp.1-10.
8. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). *Voluntary Cosmetic Registration Program – Frequency of Use of Cosmetic Ingredients*. College Park, MD; 2019. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 3, 2019; received February 13, 2019.
9. Personal Care Products Council. Updated concentration of use Information: organo-titanium ingredients (all uses reported are as a surface modifier). Unpublished data submitted by the Personal Care Products Council on January 17, 2019; 2019.
10. United States Food and Drug Administration. Color additives permitted for use in cosmetics. https://www.fda.gov/Cosmetics/Labeling/IngredientNames/ucm109084.htm. Last Updated 2018. Accessed April 27, 2018.
11. Aylott RI, Byrne GA, Middleton J, Roberts ME. Normal use levels of respirable cosmetic talc: preliminary study. *Int J Cosmet Sci*. 1979;1(3):177-186.
12. Russell RS, Merz RD, Sherman WT, Sivertson JN. The determination of respirable particles in talcum powder. *Food Cosmet Toxicol*. 1979;17(2):117-122.
13. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). 11-3-2015. Cosmetic powder exposure. Unpublished data submitted by the Personal Care Products Council.
14. Van Bommel MJ, Bernards TNM. Spin coating of titanium ethoxide solutions. *J Sol Gel Sci Technol*. 1997;8(1-3):459-463.
15. Li M, Luo B, Liu Q, et al. Synthesis of N-Acyl-N,O-acetals mediated by titanium ethoxide. *Org Lett*. 2014;16(1):10-13.
16. Schwietert CW, McCue JP. Coordination compounds in medicinal chemistry. *Coord Chem Rev*. 1999;184(1):67-89.
17. Richard Costlow Consulting, LLC. Ken-React® KR® TTS (isopropyl titanium triisostearate): summary of toxicology data for regulatory compliance. Unpublished data submitted by the Personal Care Products Council on 5-15-2018; 2018. pp. 1-5.
18. Consumer Product Testing Company, Inc. Primary ocular irritation in rabbits; Acute oral toxicity in rats (black iron oxide with 2% of isopropyl titanium triisostearate). Unpublished dta submitted by the Personal Care Products Council on 7-9-2018; 1987. pp. 1-16.
19. Collins JM, Uppal R, Incarvito CD, Valentine AM. Titanium (IV) citrate speciation and structure under environmentally and biologically relevant conditions. *Inorg Chem*. 2005;44(10):3431-3440.
20. Suwalsky M, Villena F, Norris B, et al. Structural effects of titanium citrate on the human erythrocyte membrane. *J Inorg Biochem*. 2005;99(3):764-770.
21. Tiziana G, Grazia D, Pietro R, et al. Morphological and functional alterations in human red blood cells treated with titanium citrate. *Pharmacol Pharm*. 2011;02(3):116-121.
22. Consumer Product Testing Company, Inc. Primary dermal irritation in rabbits (black iron oxide with 2% of isopropyl titanium triisostearate). Unpublished data submitted by the Personal Care Products Council on 7-9-2018; 1987. pp. 1-8.
23. ANONYMOUS. Human patch test: concealer containing 0.4% isopropyl titanium triisostearate. Unpublished data submitted by the Personal Care Products Council on 4-9-2018; 2006. pp. 1.
24. TKL Research, Inc. Human repeated patch test with challenge (eye powder containing 1.4% isopropyl titanium triisostearate). Unpublished data submited by the Personal Care Products Council on 5-8-2018; 2012. pp. 1-19.
25. TKL Research Inc. Repeated insult patch test study (foundation containing 0.433% isopropyl titanium triisostearate used as a surface modifier). Unpublished data submitted by Personal Care Products Council on 10/4/18; 2013.
26. KGL Inc. 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). Unpublished data submitted by the Personal Care Products council on 4-9-2018; 2006. pp. 1-12.
27. Clinical Research Laboratories Inc. Repeated insult patch test (foundation containing 0.348% isopropyl titanium triisostearate used as a surface modifier). Unpublished data submitted by Personal Care Products Council at 10/4/18; 2013.
28. Anonymous. Summaries of HRIPTs of products containing isopropyl titanium triisostearate used as a surface modifier. Unpublished data submitted by Personal Care Products Council on 11/07/18; 2018.

29. TKL Research. Human repeated insult patch test study of a foundation topcoat containing 0.102% isopropyl titanium triisostearate. Unpublished data submitted by the Personal Care Products Council on 4-23-2018; 2004. pp. 1-28.
30. TKL Research. Phototoxicity test of a pressed powder containing 0.004% isopropyl titanium triisostearate. Unpublished data submitted by the Personal Care Products Council on 4-23-2018; 1992. pp. 1-18.
31. Institute for In Vitro Sciences. Tissue equivalent assay with the Epiocular™ cultures (two foundation topcoats each containing 0.102% isopropyl titanium triisostearate). Unpublished data submitted by the Personal Care Products Council on 4-23-2018; 2004. pp. 1-15.
32. de Graaf N, Feilzer A, Kleverlaan C, Bontkes H, Gibbs S, Rustemeyer T. A retrospective study on titanium sensitivity: patch test materials and manifestations. *Contact Dermat*. 2018; 79:85-90.
33. National Center for Biotechnology Information. Pubchem compound database; CID=162941. Isopropyl titanium triisostearate. https://pubchem.ncbi.nlm.nih.gov/compound/162941. Last Updated 2018. Accessed April 27, 2018.
34. Brown JA. National Library of Medicine: Haz-Map. Information on hazardous chemicals and occupational diseases. *Titanium (IV) ethoxide*. https://hazmap.nlm.nih.gov/category-details?id=17412&table=copytblagents. Last Updated 2017. Accessed 1-24-2018.
35. National Center for Biotechnology Information. PubChem compound database; CID=86761841. Titanium salicylate. https://pubchem.ncbi.nlm.nih.gov/compound/86761841#section=Top. Last Updated 2018. Accessed April 27, 2018.