
Safety Assessment of Titanium Complexes as Used in Cosmetics

Status: Tentative Report for Public Comment
Release Date: January 9, 2018
Panel Date: April 8-9, 2019

All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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

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

INTRODUCTION

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

Isopropyl Titanium Triisostearate
Titanium Citrate

Titanium Ethoxide
Titanium Isostearates

Titanium Salicylate

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

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

CHEMISTRY

Definition and General Characterization

The definitions, structures, and functions in cosmetics of these ingredients are presented in Table 1.¹ The ingredients in this group are tetravalent complexes of titanium.

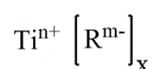


Figure 1. Generic formula of titanium complexes.

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

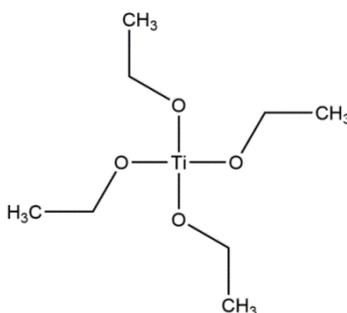


Figure 2. Titanium Ethoxide

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

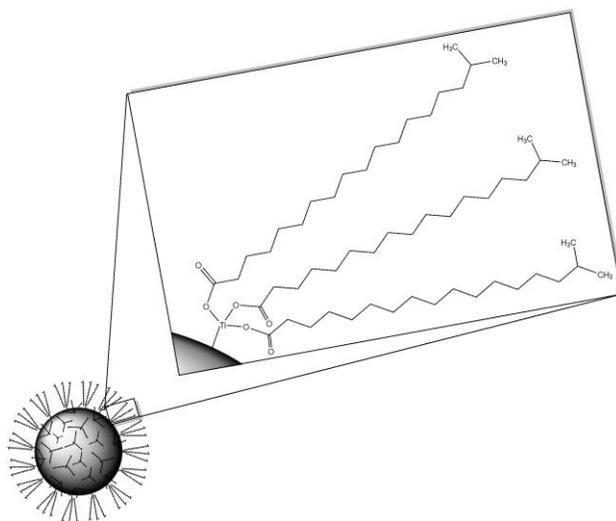


Figure 3. Idealized view of a pigment particle, surface modified by reaction with Isopropyl Titanium Triisostearate (depicted isostearyl chains are one example of an “iso”)

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

Chemical and Physical Properties

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

Method of Manufacture

Isopropyl Titanium Triisostearate

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

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

Titanium Citrate

Titanium Citrate has been prepared by mixing titanium (III) chloride with a 1.2-fold excess of sodium citrate at a pH of 3.⁶ Exposure to air resulted in the quantitative oxidation of titanium (III) citrate to colorless titanium (IV) citrate.

Composition & Impurities

Isopropyl Titanium Triisostearate

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

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

USE

Cosmetic

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

Only one of these titanium complexes 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).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 1.5% 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.

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

Cosmetic products containing Isopropyl Titanium Triisostearate may be applied to the skin or, incidentally, may come in contact with the eyes (at maximum use concentrations up to 1.5% 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.

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 Dioxide solution.¹¹ Titanium Ethoxide has also been used as a catalyst in the synthesis of *N*-acyl-*O*-ethyl-*N*,*O*-acetals.¹²

TOXICOKINETIC STUDIES

Dermal Penetration

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

Absorption, Distribution, Metabolism, and Excretion

In Vitro

Titanium Citrate

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

Human

Oral

Titanium Salicylate

Following the oral administration of titanium salicylates (~ 10 mg) to one human subject, titanium was detected in the feces and urine, with evidence that salicylate remained attached to titanium in the urine.¹³ 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, so when available, data on titanium salicylates is used throughout this report.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Isopropyl Titanium Triisostearate

The dermal toxicity of an Isopropyl Titanium Triisostearate trade name material was evaluated using New Zealand White rabbits (number of animals not stated).¹⁴ The test material was administered under a semi-occlusive wrap for 4 h. There were no signs of gross toxicity or remarkable pathology.

Oral

Isopropyl Titanium Triisostearate

The acute oral toxicity of an Isopropyl Titanium Triisostearate trade name material was evaluated using male and female Sprague-Dawley rats (number of animals not stated).¹⁴ An LD₅₀ 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%).¹⁵ 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 authors concluded that the LD₅₀ 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.¹³ 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.¹³ Details relating to the test protocol were not included.

Subchronic Toxicity Studies

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

Chronic Toxicity Studies

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

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

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

GENOTOXICITY STUDIES

In Vitro

Isopropyl Titanium Triisostearate

The genotoxicity of an Isopropyl Titanium Triisostearate trade name material (98% Isopropyl Titanium Triisostearate and < 2% isopropyl alcohol) was studied using the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, TA1537, and TA1538.¹⁴ The trade name material was tested at doses ranging from 0.2 µg to 500 µg per plate with and without metabolic activation. No increase in the number of revertants per plate was observed with or without metabolic activation.

CARCINOGENICITY STUDIES

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

ANTI-TUMORIGENICITY STUDY

Titanium Citrate

The anti-tumorigenicity of Titanium Citrate in rats was evaluated using 2 groups of 46 rats with Jensen sarcoma.^{16,13} 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.¹⁷ 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.¹⁸ For a few of the erythrocytes incubated with 0.001 mM and 0.0005 mM Titanium Citrate, the shape appeared slightly deformed when compared to controls; the cellular diameter of treated cells was described as almost normal. At a concentration of 0.0025 mM titanium citrate, most of the erythrocytes had morphological alterations. Incubation with Titanium Citrate (0.005 mM) caused damage to erythrocytes, and the cells appeared smaller and more distorted. The morphological differences between treated and control erythrocytes were statistically significant.

DERMAL IRRITATION AND SENSITIZATION STUDIES

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

Irritation

The skin irritation potential of an Isopropyl Titanium Triisostearate trade name material (98% Isopropyl Titanium Triisostearate and < 2% isopropyl alcohol) was evaluated using New Zealand White rabbits (number not stated).¹⁴ 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.¹⁹ The test substance (0.5 g, moistened with saline, under a 5 cm² occlusive patch) was applied 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.¹³ 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) was evaluated in a 24 h single insult occlusive patch test (SIOPT) involving 23 subjects.²⁰ Skin irritation was not observed in any of the subjects tested.

Sensitization

A human repeated insult patch test (HRIPT) on an eye powder containing 1.4% Isopropyl Titanium Triisostearate was performed using 101 subjects.²¹ The product was non-irritating and non-sensitizing. 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).²² 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. A foundation topcoat containing 0.102% Isopropyl Titanium Triisostearate was evaluated for its sensitization potential in an HRIPT involving 101 subjects.²³ 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.²⁴ The light source was a Xenon arc Solar Simulator (150W) with a continuous spectrum in the ultraviolet light, long wavelength (UVA; 320 to 400 nm) to mid-wavelength (UVB; 290 to 320 nm). A UVB absorbing filter that eliminated erythemogenic wavelengths (below 320 nm) was used for UVA dosing, but was removed for UVA/UVB dosing. The product (0.5 g) was applied for 24 h, under a 2 cm x 2 cm occlusive patch, to 2 separate sites (irradiated and non-irradiated). At approximately 24 h post-application (patch removal), 1 set of sites was irradiated with 24 J/cm² 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/cm² 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 was evaluated using the EpiOcular™ human cell construct (reconstructed human cornea-like epithelium).²⁵ Toxicity was measured by the reduction of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) to a blue formazan precipitate. The duration of exposure that resulted in a 50% decrease in MTT conversion in treated human cell constructs relative to control cultures (*t*₅₀) was determined (*t*₅₀ > 24 h = non-irritating). Each foundation topcoat was tested alone and as

a 50:50 mixture of the two. Human cell constructs were exposed to the test materials for up to 24 h. When the 2 foundation topcoats were tested alone, t_{50} values of 15.4 h and > 24 h were reported. The 50:50 mixture yielded a t_{50} of 15.2 h. The positive control (0.3% Triton[®]-X-100) yielded a t_{50} of 23.4 minutes. A conclusion describing the ocular irritation potential of the foundation topcoats was not stated. However, a t_{50} of < 24 h would be indicative of some degree of ocular irritation.

Animal

Isopropyl Titanium Triisostearate

The ocular irritation potential of an Isopropyl Titanium Triisostearate trade name material (98% Isopropyl Titanium Triisostearate and < 2% isopropyl alcohol) was evaluated using New Zealand White rabbits (number of animals not stated).¹⁴ The test material (0.1 ml) was instilled into the conjunctival sac, and scores for corneal opacity, iritis, and conjunctivitis were recorded at 1 h, 24 h, 48 h, and 72 h post-instillation. The following primary ocular irritation scores were reported: 10 (at 1 h), 0.7 (at 24 h), 0 (at 48 h), and 0 (at 72 h). There were no signs of gross toxicity or remarkable pathology. The test material was not corrosive.

An ocular irritation study on black iron oxide with 2% Isopropyl Titanium Triisostearate was performed using 6 New Zealand White rabbits.¹⁵ Each animal received a single “intraocular” application (0.1 g) of the test substance. The eyes remained unrinsed for 24 h after instillation. Untreated contralateral eyes served as controls. Reactions were scored according to the Draize scale at 24 h, 48 h, and 72 h post-instillation. If any of the test substance remained in the eye at 24 h, the eye was rinsed with water after the 24-h reading. The test substance was classified as a minimal ocular irritant.

OTHER CLINICAL REPORTS

Retrospective Study

Titanium Citrate

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

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

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

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

and 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).²⁶

SUMMARY

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

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 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. An Isopropyl Titanium Triisostearate trade name material is produced by reacting tetra-isopropyl titanate with 3 equivalents of isostearic acid. Methods of manufacture for the remaining titanium complexes in this safety assessment were not found. The results of an impurities analysis of a titanium compound used in the manufacture of Isopropyl Titanium Triisostearate indicated the presence of calcium (0.0003%) and titanium (16.99%).

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

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

An acute oral LD₅₀ of > 30,000 mg/kg was reported for male and female Sprague-Dawley rats (number not stated) dosed with an Isopropyl Titanium Triisostearate trade name material. 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 LD₅₀ was > 2000 mg/kg body weight, and there was no evidence of abnormalities at macroscopic postmortem examination. The injection of titanium salicylates, in water, into mice and rabbits (animal numbers and strains not stated) did not cause adverse effects.

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

An Isopropyl Titanium Triisostearate trade name material was not genotoxic to the following *Salmonella typhimurium* strains when tested at doses up to 500 µg per plate with and without metabolic activation: TA98, TA100, TA1535, TA1537, and TA1538. No published literature was found, and no unpublished data were submitted, regarding carcinogenicity for any of the titanium complexes.

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

An eye powder containing 1.4% Isopropyl Titanium Triisostearate was evaluated for skin sensitization potential in an HRIPT using 101 subjects. Neither irritation nor sensitization was observed. 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 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 was evaluated using the EpiOcular™ human cell construct (reconstructed human cornea-like epithelium). When the 2 foundation topcoats were tested alone, t_{50} values of 15.4 h and > 24 h were reported. A 50:50 mixture of the 2 topcoats yielded a t_{50} of 15.2 h. The positive control (0.3% Triton®-X-100) yielded a t_{50} of 23.4 minutes. An Isopropyl Titanium Triisostearate trade name material was classified as non-corrosive in an ocular irritation study involving 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.

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

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

DISCUSSION

Five titanium complexes are being reviewed in this safety assessment. These ingredients are all tetravalent complexes of titanium, with a high degree of covalent character in the bonds between oxygen and titanium. However, Isopropyl Titanium Triisostearate appears to be unique, as it is a reaction product with colorant particles (forming a modified surface on those particles). Of the ingredients that are being reviewed, only Isopropyl Titanium Triisostearate is being used in cosmetic products. The results of a concentration of use survey conducted by the Council indicate that this ingredient is being used at concentrations up to 1.5% 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 indicating an appreciable amount of unreacted Isopropyl Titanium Triisostearate when used as a surface modifier are provided, 28-day dermal toxicity data and genotoxicity data would then be needed to evaluate the safety of this ingredient. The same would apply to any other identified use(s) of this ingredient that would yield free Isopropyl Titanium Triisostearate in the product formulation. In light of these considerations, the Panel requested confirmation of the following: (1) Isopropyl Titanium Triisostearate is only being used as a surface modifier, (2) the other titanium complex ingredients are not being used as surface modifiers, and (3) surface modification does not result in any appreciable residual Isopropyl Titanium Triisostearate in the final product. No data have been submitted to suggest that Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, or Titanium Salicylate are used in cosmetic formulations to modify pigment surfaces in this way. Therefore, the available information suggests that these four ingredients are discrete, unreacted complexes.

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

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

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

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

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

CONCLUSION

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

**Not reported to be in use.*

TABLES

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment. ^(1: CIR Staff)

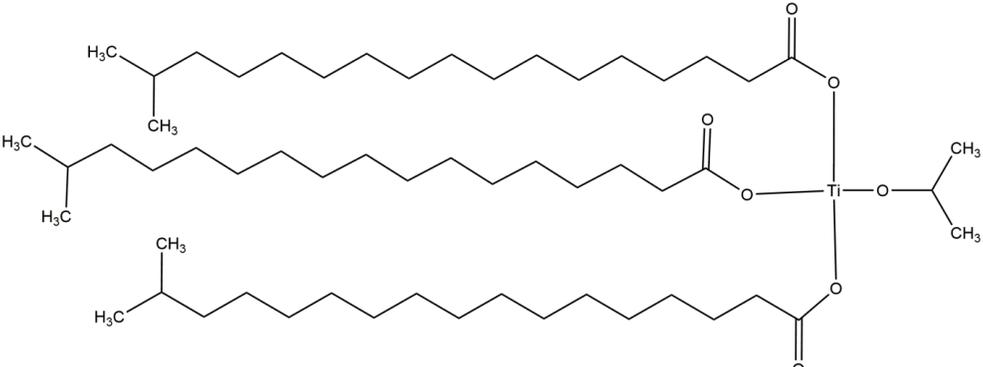
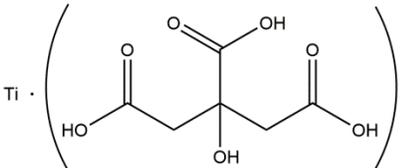
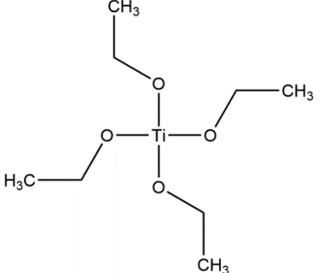
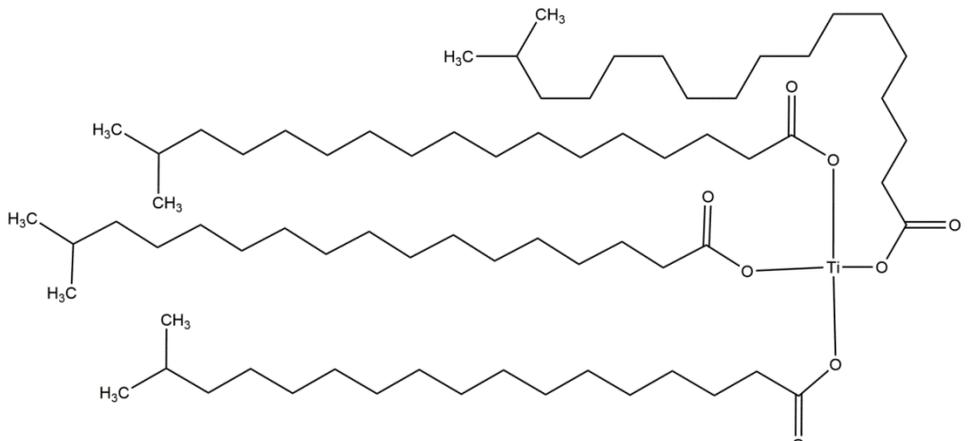
Ingredient CAS No.	Definition & Structures	Function(s)
Isopropyl Titanium Triisostearate 61417-49-0	Isopropyl Titanium Triisostearate is the organic compound that conforms to the formula: <div style="text-align: center;">  </div> <p style="text-align: center;">[However, after modification of a colorant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

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment. ^(1: CIR Staff)

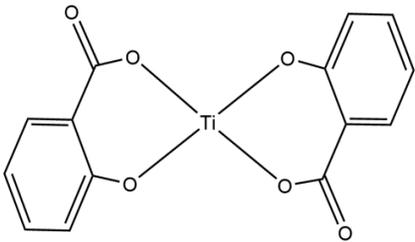
Ingredient CAS No.	Definition & Structures	Function(s)
Titanium Salicylate	Titanium Salicylate is the titanium salt of salicylic acid.	Preservatives
		

Table 2. Chemical and Physical Properties of Titanium Complexes Ingredients

Property	Value/Results	Reference
Isopropyl Titanium Triisostearate		
Form	Reddish liquid	4
Odor	Waxy fatty acid	4
Molecular Weight (Da)	961.415 (for the unreacted, discrete complex; not as a coated colorant particle)	27
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	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 light-yellow liquid	28 3
Odor	Similar to alcohol	28
Molecular Weight (Da)	228.11	
Melting Point (°C)	54	28
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	29

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

Table 4. Skin Irritation and Sensitization Studies on Titanium Complexes

Test Substance	Animals/Subjects/Cells	Test Protocol	Results
<u>Irritation (Animal)</u>			
Isopropyl Titanium Triisostearate trade name material (98% Isopropyl Titanium Triisostearate and < 2% isopropyl alcohol). Name of trade name material is synonym for discrete chemical	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. ¹⁴
Black iron oxide with 2% Isopropyl Titanium Triisostearate (colorant particles surface modified with Isopropyl Titanium Triisostearate)	6 New Zealand white rabbits	Test substance (0.5 g, moistened with saline) applied for 24 h, under occlusive patch (5 cm ²), to intact and abraded sites on opposite sides of vertebral column. Patch was secured with hypoallergenic cloth tape. Reactions scored at 24 h and 72 h post-application. Mean irritation scores averaged to determine the PII (≥ 5 = skin irritant)	PII = 0. Test substance was non-irritating to abraded and intact skin. ¹⁹
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. ¹³

Table 4. Skin Irritation and Sensitization Studies on Titanium Complexes

Test Substance	Animals/Subjects/Cells	Test Protocol	Results
<u>Irritation (Human)</u>			
Concealer containing 0.4% Isopropyl Titanium Triisostearate (colorant particles surface modified with Isopropyl Titanium Triisostearate)	23 subjects	SIOPT. Test substance (dose/cm ² not stated)	Test substance did not cause skin irritation. ³⁰
<u>Sensitization (Human)</u>			
Eye powder containing 1.4% Isopropyl Titanium Triisostearate (colorant particles surface modified with Isopropyl Titanium Triisostearate)	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. ²¹
Foundation containing 0.4% Isopropyl Titanium Triisostearate (colorant particles surface modified with Isopropyl Titanium Triisostearate)	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. ²²

Table 4. Skin Irritation and Sensitization Studies on Titanium Complexes

Test Substance	Animals/Subjects/Cells	Test Protocol	Results
Foundation topcoat containing 0.102% Isopropyl Titanium Triisostearate (colorant particles surface modified with Isopropyl Titanium Triisostearate)	101 subjects	HR IPT. 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. ²³

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