Scientific Literature Review

Tin and Tin Oxide as Used in Cosmetics

February 17, 2012

All interested persons are provided 60 days from the above date to comment on this Tentative Report and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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 Director, Dr. F. Alan Andersen.

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Manager/Lead Specialist.

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INTRODUCTION

Published and unpublished data relevant to evaluating the safety of tin oxide and tin as used in cosmetics are summarized in this literature review. Tin oxide functions as an abrasive, bulking agent, and opacifying agent and tin functions as a surface modifier in cosmetic products.[1]

CHEMISTRY

Definition and Structure

As given in the *International Cosmetic Ingredient Dictionary and Handbook*,[1] tin oxide (CAS Nos. 1332-29-2 and 18282-10-5), the dioxide of tin, is an inorganic oxide that conforms to the following structure:

Other names for this chemical include: stannic oxide, white tin oxide, tin dioxide, stannic anhydride, and flowers of tin.[1,2]

Tin (CAS No. 7440-31-5) is a metallic element with the symbol Sn.

Physical and Chemical Properties

Tin is a silver-white metal that is malleable and somewhat ductile. It has a highly crystalline structure and exists in two allotropic forms at normal pressures. Gray tin exists below 13.2 °C and has a cubic structure. At 13.2 °C, gray tin is converted to white tin, which has a tetragonal structure.[3,4] The white form is known as the common, stable form at room temperature.[5] In compounds, tin can exist in the +2 or +4 oxidation state.[3,4] In compounds, tin in divalent and tetravalent oxidation states are designated as stannous and stannic, respectively. The Stock Oxidation-Number system denotes the oxidation state using Roman numerals in parentheses following the metal's name: tin(II) and tin(IV).[6] The cosmetic ingredient, tin oxide is tin(IV) oxide.

Chemical and physical properties of Tin and Tin Oxide are found in Table 1.

Method of Manufacture

The earth's crust contains approximately 2 to 3 ppm tin, comprising 0.0006% of the earth's crust.[2,7] The most important tin-containing mineral is cassiterite, SnO_2. Other tin minerals are stannite, teallite, cylindrite, and canfieldite. After tin-containing ores are mined, they undergo further separation processing, resulting in concentrates containing 70–77% tin by weight, almost pure cassiterite, and are ready for smelting.[8] Elemental tin is obtained from cassiterite by reduction with coal in a reverberatory furnace.[5] Although tin oxide occurs naturally in mineral form, this is not the source of the commercial product. It is manufactured directly from tin metal by thermal oxidation (from mined or recycled tin), either by exposing molten tin to air in a furnace at elevated temperatures, or by blowing tin powder in a stream of air through a furnace at approximately 700°C.

According to one source, the commercial production of tin oxides yielded the following grades: average particle size of 0.3 µm (bulk density = 0.72 g/cm^3), average particle size of 0.4 µm (bulk density = 1.15 g/cm^3), and average particle size of 0.5 µm (bulk density = 1.35 g/cm^3).[9] Each grade is > 99.0% pure and has a specific gravity of 6.9.

Impurities

Commercially available metallic tin is approximately 99.8% pure.[5]

USE

Cosmetic

Tin oxide functions as an abrasive, bulking, and opacifying agent and tin functions as a surface modifier in cosmetic products.[1] According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2011, tin oxide was being used in cosmetic products, whereas, elemental tin was not.[10] These data are summarized in Table 2. Results from a survey of ingredient use concentrations provided by the Personal Care Products Council (also included in Table 2) in 2011 indicate that tin oxide was being used at concentrations up to 1% (rinse-off products) and up to 5 % (leave-on products).[11]

Cosmetic products containing tin oxide may be applied to the skin and hair, or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Tin oxide is used in dusting powders and cosmetic sprays, other fragrance preparations, and body and hand sprays, and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm when compared with pump sprays.[12,13] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal region and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[14,15] However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects, depending on their chemical and other properties.

Noncosmetic

Tin(IV) oxide is used in a variety of manufacturing applications, including polishing glass and other metals.[2] Elemental tin is present mainly in solder alloys used in the electronics industry, and is also used as a protective coating for other metals, especially those used for food containers.[16] Foods usually contain tin at levels < 4 μg/g, but higher levels may be found in processed foods because of tin-based preservatives and stabilizers and/or leaching from containers.[17] The Food and Agriculture Organization of the World Health Organization's Joint Expert Committee on Food Additives has established a provisional tolerable weekly intake of 14 mg Sn/kg body weight.[18] The European Union has established maximum levels for certain contaminants, inorganic tin included, to achieve a high level of public health protection, especially for sensitive population groups such as children or individuals with allergies.[19] Maximum levels of 200 mg/kg and 100 mg/kg were established for inorganic tin in canned foods and canned beverages, respectively.

TOXICOKINETICS

Oral Studies

Tin

After a single gavage dose of 20 mg/kg body weight of radiolabeled ^{113}Sn(II) or ^{113}Sn(IV) as the fluoride or citrate**,** the tissue distribution of tin in female Charles River (CD) or Cox Charles River rats after 48 h as a percentage of the administered tin(II) or tin(IV), respectively, was as follows: 1.0% and 0.24% (skeleton), 0.08% and 0.02% (liver), and 0.09% and 0.02% (kidneys).[20] Female rats excreted 95% of the radiolabeled tin in the feces and less than 1% in the urine. When oral tin doses of 20 mg/kg body weight were administered 6 days/week for 4 weeks, only the bone contained higher tin concentrations after day 28 when compared to tin concentrations after day 1. The half-life of tin in the femur was estimated to be 34 to 40 days. It was concluded that, of the soft tissues, only liver and kidneys were likely to accumulate significant amounts of tin as a result of the oral ingestion of tin salts. ^{113}Sn was found in the brain of rats at 48 h post-administration of ^{113}Sn(II) or ^{113}Sn(IV) (as the citrate or fluoride) as a single oral dose (4 mg), as oral doses of 20 mg/kg body weight on 6 days/week for 4 weeks, or as a single i.v. dose (0.4 mg).

Tin(II) chloride was injected orally (intagastric [i.g.], using stomach tube) into mice, Sprague-Dawley rats, African white-tailed rats, monkeys, and dogs.[21] Less than 5% was absorbed from the gut, and bone was the chief site of tin deposition.

The absorption of tin from the gastrointestinal tract and its distribution in the tissues was studied using groups of male Wistar rats dosed orally(gastric intubation) with ^{113}Sn(II) chloride together with the following other food components: sucrose, ascorbic acid, and potassium nitrate (given with the tin salt either separately or together), ethanol (given as 20% solution), a solution of albumin, and an emulsion of sunflower oil and 1% Tween 20.[22] In all groups, 90% to 99% of the administered radioactivity was excreted in the feces within 48 h, at which time fecal excretion and retention in the alimentary tract accounted for 98.7% to 99.9% of the dose. Only traces of ^{113}Sn were detected in organs and tissues examined, irrespective of the other components administered with the tin salt.

In another study, rats reportedly absorbed 7.65% of a single oral dose of tin(IV) chloride.[23] The recovery of 99% of administered tin in the feces and the lack of detectable urinary tin in the 24 h following ingestion of tin (7 to 20 mg/kg body weight) in orange juice by rats and cats indicated very low gastrointestinal absorption of tin.[24]

The concentrations of tin in the tibias (µg/g) of rats fed diets supplemented with tin(II) chloride (100 to 2,000 mg of tin per kg of diet) were more than 5 times greater than the tin concentrations in the kidneys and nearly 20 times greater than the concentrations in the liver.[25] No other organs were analyzed. Tin accumulated in the tibia and kidneys in a dose-dependent manner.

Male Wistar rats were given either 100 mg $SnCl_2$ per liter (0.44 mM), 250 mg/l (1.11 mM) or 500 mg/l (2.22 mM) in drinking water for 18 weeks.[26] Control rats received tap water. The tin content of the right cerebral hemispheres ranged from 5 to 10 pmol/g wet weight in control rats, and the following ranges were reported for the remaining groups: 7 to 19 pmol/g wet weight (0.44 mM in drinking water), 5 to 22 pmol/g (1.11 mM in drinking water), and 16 to 60 pmol/g (2.22 mM in drinking water). At the highest dose (2.22 mM), tin accumulated in the cerebrum throughout the experiment. In the right cerebral hemispheres, tin concentrations greater than the 1.11mM dose were only found after 15 and 18 weeks. Tin did not increase in the right cerebral hemispheres after dosing with 0.44 mM. After one week at the highest dose (2.22 mM), blood tin increased promptly, and there was no evidence of further accumulation. Blood tin at the 0.44 mM dose level did not differ from controls. Effects on cerebral and muscle acetylcholinesterase activity reported in this study are included in the Toxicology section later in the report text. Data from other animal studies suggest that inorganic tin does not readily cross the blood-brain barrier.[21,27,26]

Studies with the radioactive tin isotope ^{113}Sn were performed using rats and rabbits to determine the kinetics of tin and of its absorption and excretion following oral administration.[28] The absorption of tin in the gastrointestinal tract was small and was dependent upon the amount administered. An increased uptake of tin was not found in any organ; absorbed tin was excreted via the kidneys. This information is from an English summary of a German publication. Additional details will be included after this publication has been translated.

Eight healthy volunteers were fed mixed diets containing 0.11 mg tin (control diet) and 49.67 mg tin (test diet) daily for 20days. [30] The tin content of the control diet was typical of that found in diets that contained fresh and frozen foods. The tin content of the test diet was typical of the amount found in diets that containing several servings of certain canned foods. When fed the test and control diets, 3% and 50% of their dietary tin intake, respectively, was absorbed .

When 9 healthy volunteers were given diets consisting of fresh foods (10 mg tin per day), or cold-stored canned foods (26 mg of tin per day), or warm-stored canned foods (163 mg of tin per day) for 24 days, fecal excretion accounted for the whole dose, and none was detected in the urine.[31]

Four human volunteers (2 males, 2 females) with tin blood levels of < 2 ng/ml (< 17 nmol/liter) each consumed 60 mg of tin in fruit juice from an unlacquered can, and blood samples were taken after 2 h, 5 h, and 24 h.[32] The 2 females had detectable tin blood levels (3 ng/ml) only in the 5-h blood samples. However, the 2 males had peak blood tin concentrations of 4.7 ng/ml after 2 h and 3.9 ng/ml after 24 h.

Intravenous/Intraperitoneal Study

Intravenous (i.v.) dosing of ^{113}Sn(II) or ^{113}Sn(IV) (each as the citrate) in rats resulted in the excretion of significant fractions of administered tin in the urine. [20] The presence of tin in the feces after i.v. dosing indicated that the biliary system can contribute significantly to tin clearance.

Tin(II) chloride was injected by intraperitoneal (i.p.), and intravenous (i.v.) routes into mice, Sprague-Dawley rats, and African white-tailed rats and i.v. into monkeys and dogs.[21] Less than 5% was absorbed, and bone was the chief site of tin deposition.

Subcutaneous Study

Ten female Wistar rats received repeated subcutaneous (s.c.) doses (2 mg Sn/kg) of tin(II) chloride every other day (7 doses total).[33] A second group of animals was exposed (same method) to tin(II) chloride labeled with ^{113}Sn. The control group consisted of 6 rats. The animals were killed 24 h after the last dose. Approximately 60% of the metal was retained in the body. Of this amount, approximately 95% accumulated in the skin and hair. The total dose of tin administered in the study was approximately 3,400 µg/animal, of which an average of 2,035 µg was retained. In the remaining organs and tissues, tin concentrations (expressed as µg Sn/g tissue) were lower by 1 to 2 orders of magnitude, which corresponded to 2.57 to 0.0001% of the retained dose. Most of the ^{113}Sn was retained in the kidneys (0.20 ± 0.35 µg Sn/kg) and muscles + bones (0.59 ± 0.18 µg Sn/kg).

PBPK Model

According to The International Commission on Radiological Protection (ICRP) physiologically based pharmacokinetic (PBPK) model,[34] the fraction of ingested tin that is absorbed from the gastrointestinal tract (uptake to blood) is assumed to be 0.02. Absorbed tin is assumed to enter the blood, from where 50% is immediately transferred to excreta (specific routes not specified in the model), 35% is transferred to bone mineral, and 15% is uniformly distributed to all other tissues. Tin in any tissue or organ is retained with elimination half-times of 4 (20% of tissue burden), 25 (20%), and 400 (60%) days.

The ICRP also provided classifications for clearance of inhaled tin compounds in the respiratory tract, for use in an inhalation model.[29,34] Sulfides, oxides, hydroxides, halides, and nitrates of tin, and stannic phosphate were assigned Type M, and all other tin compounds were assigned to Type F. With Type F compounds, rapid absorption (100%) is assumed to occur within 10 minutes of material deposition in the bronchi (BB), bronchiole (bb), and alveolar interstitial (AI) regions. Fifty percent of Type F compounds deposited in the extrathoracic region transfer to the gastrointestinal tract (ET_2). During breathing through the nose, approximately 25% of the tin deposited in the extrathoracic region is absorbed rapidly, and breathing through the mouth yields 50% absorption. With Type M compounds, approximately 70% of the tin deposited in AI regions is eventually transferred to the blood, approximately 10% of the tin deposited in BB and bb is absorbed rapidly, and 5% of the tin is deposited in ET_2. During breathing through the nose, approximately 2.5% of the tin deposit in the extrathoracic region is absorbed rapidly and 5% is absorbed rapidly during breathing through the mouth.

Bioavailability

Overall, the oral, intravenous, subcutaneous and the modeling data for tin suggest that this element is not bioavailable to any great extent. CIR is aware of additional studies on the bioavailability of tin and tin compounds in the published literature.[35,36,37,38] Relevant information from these studies will be added at the draft report stage.

TOXICOLOGY

Acute Toxicity

Parenteral Studies

Tin

Reportedly, the results of studies in which animals (species not stated) were injected intravenously (i.v.) with tin indicated a lethal dose of 100 mg/kg body weight.[39]

Using a laryngeal tube, tin dust (50 mg, in saline) was injected into the trachea of rats (number and strain not stated) and then blown into the lungs.[40] At 3 months post-injection, microscopic examination revealed many areas with dust cells lining the alveoli. Tin particles were observed in phagocytes, in the pleural lymphatics, and in the mediastinal lymph glands. In another experiment, tin dust was injected i.v. into the tail vein of mice (number and strain not stated). Particles of tin dust

were found in the lungs, spleen, and, particularly, in the liver. No cellular reactions were observed and all mice were very healthy. In both mice and rats, no fibrous response in the lungs was observed up to a year post-evaluation.

Repeated Dose Toxicity

Oral Studies

Tin Oxide

Various tin compounds were fed to weanling Wistar rats for either 4 or 13 weeks. Groups of 10 males and 10 females were fed diets containing 0, 0.03, 0.10, 0.30, or 1.0% of the following: tin(IV) oxide, tin(II) chloride, tin(II) orthophosphate, tin(II) sulfate, tin(II) sulfide, tin(II) oleate, tin(II) oxalate or tin(II) tartrate for 28 days.[41] Additional groups of 10 males and 10 females were fed either tin(II) chloride or tin(II) oxide in the diet at the levels previously mentioned for 90 days. Endpoints monitored included: mortality, growth, food consumption and utilization, hematology, urinalysis, serum biochemistries, and gross and microscopic pathology. No compound-related adverse effects were observed among rats fed tin(IV) oxide, tin(II) sulfide, or tin(II) oleate for 4 weeks. Anemia and reductions in growth, food consumption and food use efficiency were observed, however, among rats fed either 0.3 or 1% of tin(II) chloride, tin(II) orthophosphate, tin(II) sulfate, tin(II) oxalate, or tin(II) tartrate. Microscopic evidence of liver damage (homogeneous liver cell cytoplasm; slight but definite oval cell type hyperplasia of bile ducts) was also observed in male and females fed 1.0% of the same compounds. Similar hepatic changes, though of lesser intensity and frequency, were observed among rats fed 0.3% tin(II) chloride, tin(II) oxalate or tin(II) orthophosphate. Females given tin(II) orthophosphate had a dose-related increase in relative liver weight at $\geq 0.1\%$.

No compound-related adverse effects were observed among rats fed tin(II) oxide for 13 weeks. In the 13-week study with tin(II) chloride, rats fed 1.0% were killed after 8 weeks on test because of high mortality. Necropsy of these rats revealed anemia, distinct liver changes (described above), severe pancreatic atrophy, enteritis, moderate testicular degeneration, " a spongy state of the white matter of the brain", and acute broncho-pneumonia. It was speculated that some of these changes were due to starvation. Poor appetite and reduced growth were also observed among rats fed 0.3% stannous chloride, but these changes were observed only for the first 2 weeks. Thereafter, growth and food consumption among rats fed 0.3% were similar to controls. Slight anemia (males only) and other changes (described above) were also observed among rats fed 0.3%. No compound-related adverse effects were observed among rats fed 0.03 or 0.1% tin(II) chloride for 13 weeks. The authors concluded that 0.1% of tin compounds in the diet (22 to 33 mg of tin/kg/day; estimated by investigators) was a "no-effect-level." [41]

Tin

The tolerability of tin migrated from canned food (tomato soup) packaging at concentrations < 0.5 mg/kg (tomato soup without tin) and 201 mg Sn/kg and 267 mg Sn/kg in 250 ml tomato soup was evaluated using 24 normal volunteers.[42] Tomato soup samples (250 ml) were heated to the temperature range of 65ºC to 70ºC and consumed within 15 minutes after nominal dosing time (8:00 a.m.) in a 3-way crossover design with wash out periods of at least 48 h between the different dose levels. There were 3 treatment periods, and the subjects were evaluated for adverse effects at 4 h post-dosing. No clinically significant adverse effects were reported. Similarly, no toxic effects were observed when 9 volunteers were given canned food with tin concentrations of 13, 33, and 204 mg/kg for three 24-day periods, respectively.[31] However, toxicity (e.g., nausea, vomiting, and diarrhea) in humans due to the consumption of food highly contaminated with tin has been reported.[5,43,24,44,45,46]

At the 64th Joint FAO/WHO Expert Committee on Food Additives (JECFA) meeting in 2005, the Committee reiterated its opinion, expressed at the 33rd and 55th Committee meetings, that the available data for humans indicated that inorganic tin at concentrations > 150 mg/kg in canned beverages or > 250 mg/kg in canned foods may produce acute gastric irritation in certain individuals.[16] Therefore, ingestion of inorganic tin at concentrations equal to the proposed standard for canned beverages (200 mg/kg) may lead to adverse reactions.

Cytotoxicity

Metallic tin (powdered form; particle size = < 125 µm) was not cytotoxic in an *in vitro* cell culture test involving human fibroblasts incubated for 24 h.[47]

Effect on Acetylcholinesterase

Male Wistar rats were given either 100 mg $SnCl_2$ per liter (0.44 mM), 250 mg/l (1.11 mM) or 500 mg/l (2.22 mM) in drinking water for 18 weeks.[26] At the 2 higher doses, tin exposure caused a dose-dependent increase in cerebral (left cerebral hemispheres) and muscle acetylcholinesterase activity.

Respiratory Irritation

Reportedly, tin powder is moderately irritating to the airways.[39]

Ocular Irritation

Tin Oxide

The ocular irritation potential of an eyeshadow containing 0.3% tin oxide was evaluated using 34 female subjects (18 to 65 years old), 3 of whom withdrew for reasons unrelated to conduct of the study.[48] The participants were instructed to use the test material at least once daily for 4 weeks. A comprehensive ocular examination was performed at the end of the 4-week period. There were no adverse events, and all ophthalmologic examinations remained within normal limits. Study results did not indicate a potential for ocular irritation or hypersensitivity.

Tin

Reportedly, tin powder is moderately irritating to the eyes.[39]

Skin Irritation and Sensitization

Tin Oxide

The skin irritation and sensitization potential of a powder eye shadow containing 0.3% tin oxide was evaluated in a repeated insult patch test (RIPT) using 111 male and female subjects (18 to 75 years old), 98 of whom completed the study.[49] Withdrawal from the study was not related to application of the test material. A 1" x 1" semi-occlusive patch containing 0.2 g of the test material was applied to the upper back (between the scapulae) of each subject 3 times per week for a total of 9, 24 h induction applications. After a 2-week non-treatment period, challenge patches were applied for 24 h to a new test site. Reactions were scored at 24 h and 72 h post-application. No reactions were observed, and it was concluded that the test material did not have skin irritation or allergic contact sensitization potential.

The skin irritation and sensitization potential of a lipstick containing 0.5% tin oxide was also evaluated in an RIPT (same procedure) using 112 male and female subjects (16 to 79 years old), 103 of whom completed the study. Withdrawal from the study was not related to application of the test material. No reactions were observed, and it was concluded that the test material did not have the potential for causing dermal irritation or allergic contact sensitization.[50] In another study, the skin irritation and sensitization potential of a lipgloss product containing 0.35% tin oxide was evaluated in an RIPT (amount per patch not stated) using 112 male and female subjects (18 to 70 years old), 108 of whom completed the study.[51] The test protocol was identical to that used in the preceding test, with the exception that challenge sites were evaluated at 24 h, 48 h, and 72 h post-application. No reactions were observed, and it was concluded that the test material did not demonstrate a clinically significant potential for eliciting dermal irritation or sensitization.

Tin

Seventy-three nickel-sensitive patients (age range not stated) were patch-tested with copper discs (12 mm diameter) plated with a tin coating.[52] The discs were applied directly to skin of the upper back and secured with Scanpor® tape for 48 h. Reactions were scored at 48 h and 72 h post-application. Positive reactions were observed in 6 subjects (age range: 7 to 74 years). Five subjects had a ++ allergic reaction and 1 subject had a +++ allergic reaction to the tin discs. An additional 4 subjects were classified as having doubtful reactions. Patch test results also indicated that it is unlikely that metallic tin is a skin irritant. It was noted that if pure metallic tin were an irritant, one would have expected a higher number of doubtful reactions.

Allergenicity

Intraperitoneal (i.p.) or intravenous (i.v.) injections of metallic tin powder (200 mg in saline) produced a striking plasmacellular hyperplasia in the draining lymph nodes and spleen of Lewis rats.[53,54] The lymph node response to metallic tin varied from a very mild response to insoluble foreign particles to a marked granulomatous hyperplasia (August rats) and intense plasmacellular hyperplasia (Lewis rats and F_1 hybrids of Lewis rats).[55]

Occupational Studies/Case Reports

Tin Oxide

Two-hundred fifteen workers (ages not stated) were exposed to tin oxide fumes at a plant, 95% of whom had at least 3 years of service.[56] Of the 215 workers that received chest X-rays, 121 had changes identified as pneumoconiosis. None of the X-ray films were suggestive of massive fibrosis or significant emphysema, and there was no evidence of massive fibrosis or nodulation. There were no differences in the following between the 121 pneumoconiotic workers and 94 non-pneumoconiotic workers: respiratory symptoms, vital capacity, chest expansion, loss time due to chest illness, and incidence of tuberculosis.

A clinical study of 19 male employees (most < 30 years old) exposed to tin oxide dust and fumes at a plant was performed.[57] Impairment of pulmonary function was not observed in any of the subjects, and there were no reports of work disability from any clinical cause. Physical examinations did not reveal any abnormal lung findings or significant findings in general. All of the values for vital capacity, maximal breathing capacity, resting minute volume, and respiratory reserve were within normal limits. The absence of alteration in these ventilatory tests indicae that there was no significant degree of obstructive emphysema or of diffuse pulmonary fibrosis. Based on the methods used, it was noted that the only type of pulmonary function alteration that could have escaped detection would have been impaired diffusion of the alveolo-capillary block type, which is found in cases of asbestosis and berylliosis.

Based on chest roentgenograms, one subject was classified as completely normal, 8 were classified as stannosis suspects, and 10 were classified as having tin oxide pneumoconiosis. It was noted that subjects with less than 3 years of exposure may be classified as either normal or suspects, but do not present with pulmonary nodulation. After 3 years of exposure to tin oxide, nodular stenosis was found in all cases, and advanced stages occurred with increasing frequency as the years of exposure increased. Of the 10 employees with roentgenographic changes classified as stannosis, 6 had been exposed to tin oxide fume. The most advanced changes were observed in 4 of these 6 employees. One of the 4 subjects probably had been exposed exclusively to tin oxide dust and had first stage stannosis, and the remaining 3 subjects (exposure to dust and fumes) had varying degrees of change. Six of the 10 employees with lung changes were asymptomatic and the following signs were reported for the remaining 4: moderate anorexia (2 subjects), cough with serious expectoration (1 subject), and scapular pain (1 subject). For the 10 cases of stannosis, the hemograms and sedimentation rates were within normal limits. Traces of albumin in the urine were reported for 3 of the cases, and the blood Kahn reaction was normal in all cases. The authors noted that the results of this study corroborate the conclusion that tin oxide fume, and not tin oxide dust, is more likely to be the cause of stannosis.[57]

Stannosis is the form of pneumoconiosis (non-fibrotic form) that results from the inhalation of tin in the form of tin oxide fumes or dust. Tin oxide accumulates in the pulmonary parenchyma. Lung radiography results for a man (age not stated) who had worked in the smelter of a tin mine for 26 years revealed moderately profuse small nodules, some of which were metallic in density.[58] The patient was asymptomatic and clinically normal. Lung function tests were not performed. Results 8 years later revealed an increase in the profusion of small opacities, particularly in the left mid-zone of the lung. The patient remained asymptomatic. Another case report involved a 55-year-old male employee of a detinning plant for 15 years. He was exposed to tin fumes as well as clouds of coal dust on the job, and lung function test results yielded a forced vital capacity of 90% and a forced expiratory volume that was 96% of predicted values. Lung radiography results revealed very profuse bilateral nodules (~ 3 mm in diameter). At lung biopsy, focal aggregations of macrophages containing dust particles (black particles) were observed in some of the air spaces and in the perivascular and peribronchiolar connective tissue. Electron probe analysis results indicated that tin was present in the dust.[58]

A 50-year-old female (non-smoker) with stannosis was exposed to tin fume for 33 years. There were also exposures to biomass fuels and asbestos. A chest X-ray revealed common nolular lesions and thorax high resolution computed tomography revealed widespread interlobular thickening and peribronchial thickening. Subpleural nodules with metallic density were observed in the upper and middle lobe of the right lung. Bronchial lavage cytology was defined as class II, and histiocytic cells and focal fibrosis were detected on transbronchial lung biopsy. The patient died 6 months later due to respiratory failure.

Tin

Fifty workers in the ceramics industry (12 males, 38 females) were patch tested with 2.5% metallic tin. A positive reaction was observed in only one subject. [59]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Tin

The placental transfer of tin was studied using groups of 12 pregnant Sprague-Dawley rats. Fetal tin values were slightly elevated (0.8 to 1.3 mg/kg body weight) in Sprague-Dawley rats on day 20 of gestation when the maternal diets contained tin salts (tin(II) fluoride, sodium pentachlorostannite, or sodium pentafluorostannite) at 125 to 625 mg/kg in the feed (approximately 10 to 50 mg of tin per kg body weight per day).[60] The increases were generally dose-related. Untreated rats had fetuses containing 0.64 mg of tin per kg body weight. Reproductive performance was normal in all dietary groups, and the number of viable fetuses per litter ranged from 9 to 14. Only one nonviable (unresorbed) fetus was observed in the 154 females that delivered viable fetuses.

The levels of trace elements in maternal blood, umbilical cord blood, and the placenta were studied using 198 female subjects (16 to 39 years old) who, collectively, were from areas of the United States identified as the Southeast (Charlotte and Birmingham), NewYork-New Jersey (Riverhead and Elizabeth), Utah (Ogden and Salt Lake City), and California (East and West Los Angeles).[61] All participants lived in their respective areas for at least the entire duration of pregnancy. Blood/tissue specimens were obtained from obstetrics departments in local hospitals, and 25 maternal-fetal sets were collected from each of the 8 areas. Venous blood specimens were collected from the mother after delivery. Umbilical cord blood specimens were drawn after the cord was cut, but before delivery of the placenta. Samples of the placenta (free of gross pathology) consisted of 3 peripheral wedges cut in full thickness after placental delivery. Sample sizes ranged from 177 to 187 for cord and maternal blood and 160 to 169 for the placenta. Mean blood levels of tin were 4.6 µg/100 ml blood (maternal blood) and 5.6 µg/100 ml blood (cord blood). The mean level of tin in the placenta was 5.0 µg/100 g.

GENOTOXICITY

Tin Oxide and Tin Ore Powder

Tin(IV) oxide and 5 kinds of Yunnan tin ore powder were administered to rats through the trachea, and cytological preparations were made at various intervals in order to determine effects on micronucleus frequency and karyorrhexis of rat bone marrow cells and lung macrophages.[62] Results indicated that tin(IV) oxide and each of the 5 kinds of Yunnan tin ore powder can induce micronuclei and karyorrhexis in bone marrow cells. On the first and tenth day, the frequency of karyorrhexis was higher than that of micronuclei, and differed significantly from that of the control, and vice versa, on the 20^{th} and 30^{th} days. Tin(IV) oxide and each of the 5 kinds of Yunnan tin ore powder also can induce micronuclei and karyorrhexis in lung macrophages. On the 10^{th} and 20^{th} days, the frequency of karyorrhexis was the same as that in bone marrow cells.

CARCINOGENICITY

Tin

Tin foil imbedded s.c. in the abdominal wall, just ventral to the fascia of 25 male Wistar rats did not induce tumor formation (monitored weekly for 300 days) in any of the animals.[66]

Tin foil inserted subcutaneously into 39 male Marsh mice did not result in local neoplasms in any of the mice over the course of 19 months.[67]

An intrathoracic injection of a suspension of tin needles into each of 43 male Marsh mice did not induce local or general neoplasm development over the course of 19 months.[68]

HEALTH EFFECTS ASSESSMENT

According to a health effects assessment on tin and tin compounds by the U. S. Environmental Protection Agency, an oral reference dose (RfD) of 0.62 mg Sn/kg/day or (43.4 mg Sn/day) was recommended.[66] The RfD is defined as an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan.

In a toxicological profile for tin and tin compounds, prepared by the Agency for Toxic Substances and Disease Registry of the U.S. Department of Health and Human Services, a minimal risk level (MRL) of 0.3 mg/kg/day was derived for intermediate-duration oral exposure (15 to 364 days) to inorganic tin.[29] An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure.

In a Belgian case-control study (n = 272 men and women), a significantly increased risk (odds ratio 3.72, 95% confidence interval 1.22 to 11.3) of chronic renal failure was found for occupational exposure to tin (Nuyts et al. 1995). [67] Exposures were reconstructed from self-reported occupational histories by 3 industrial hygienists independently.

The National Institute for Occupational Safety and Health (NIOSH) has established a recommended exposure limit for tin and tin (IV) oxide of 2 mg/m^3 of air as a time-weighted average for up to a 10-h workday during a 40-h work week.[68]

SUMMARY

The safety of tin oxide (dioxide of tin) and elemental tin in cosmetics is reviewed in this report. Elemental tin is obtained from cassiterite by reduction with coal in a reverberatory furnace. Tin oxide is manufactured directly from tin metal by thermal oxidation. According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2011, tin oxide, but not elemental tin, was being used in cosmetics. Furthermore, results from a survey of ingredient use concentrations provided by the Personal Care Products Council in 2011 indicate that tin oxide was being used at concentrations up to 1% in rinse-off products and up to 5% in leave-on products.

The results of toxicokinetic studies involving rats, cats, monkeys, and dogs indicated that more than 90% of orally or parenterally (i.v. and i.p.) administered tin (as tin salts) was excreted. The skeleton was the main site of deposition, but tin was also deposited in the liver and kidneys. There was also very little absorption of tin from the GI tract of man. Following s.c. dosing in rats, approximately 60% of the metal was retained in the body. Of this amount, approximately 95% accumulated in the skin and hair. PBPK modeling (ingestion) indicated that tin in any tissue or organ is retained with elimination half-times of 4 (20% of tissue burden), 25 (20% of tissue burden), and 400 (60% of tissue burden) days. An inhalation model for tin compounds (oxides included) indicated that 70% of the tin was deposited in alveolar interstitial regions and eventually transferred to the blood. Approximately 10% of the tin deposited in the bronchi and bronchioles was absorbed rapidly.

Reportedly, i.v. dosing of animals yielded a lethal dose of 100 mg/kg body weight. No test substance-related adverse effects were observed in rats fed tin(IV) oxide at dietary concentrations up to 1.0% for 4 or 13 weeks. Toxic effects were not observed in 9 volunteers given canned food that yielded a maximum dose of 204 mg Sn/kg over a 24-h period. Elemental tin was not cytotoxic to human fibroblasts *in vitro*.

Reportedly, tin powder is moderately irritating to the airways. An eyeshadow containing 0.3% tin oxide did not cause ocular irritation in 31 subjects who participated in a 4-week product use study (daily applications). In repeated insult patch tests, neither a lipstick (0.5% tin oxide, 103 subjects), lipgloss product (0.35% tin oxide, 108 subjects), nor a powder eye shadow (0.3% tin oxide, 98 subjects) induced skin irritation or allergic contact sensitization. Of 73 nickel-sensitive patients patch-tested with copper disks plated with a pure tin coating, 6 had allergic reactions and 4 had doubtful reactions. Tin was not classified as a skin irritant. Intraperitoneal or i.v. injections of metallic tin powder (200 mg in saline) induced plasmacellular hyperplasia in the spleen and draining lymph nodes.

In occupational settings, stannosis has been observed in workers exposed to tin oxide fumes. In a case-control study (272 men and women), a significantly increased risk (odds ratio = 3.72) of chronic renal failure was found for occupational exposure to tin. A positive reaction was observed in 1 of 50 workers in the ceramics industry patch-tested with 2.5% metallic tin.

In pregnant rats, dietary exposure to tin salts resulted in a dose-related elevation (0.8 to 1.3 mg/kg body weight) of tin values in fetuses. Tin in maternal blood, umbilical cord blood, and the placenta was detected in a study involving 198 female subjects from various areas of the United States.

Tin(IV) oxide administered intratracheally induced micronuclei and karyorrhexis in rat bone marrow cells *in vivo*. The s.c. implantation of tin foil into the abdominal wall of 25 rats did not induce malignant tumor formation during the 300-day latent period necessary for tumor formation. Local neoplasms also did not develop during a 19-month observation period after 39 mice were surgically implanted with pure tin foil. Similarly, over the same observation period, neither local nor general neoplasm development was noted in any of 43 mice injected intrathoracically with a tin needle saline suspension over a period of 19 months.

DATA NEEDS

Additional data that may be useful in addressing the safety of these ingredients as used in cosmetics include:

1. Dermal penetration of tin and tin oxide, preferably from actual or representative cosmetic formulations.
2. Information on the particle size of tin and tin oxide as used in cosmetics, particularly identification of any nano-sized particles.

Table 1. Properties of Tin Oxide and Tin[69]

Chemical	Form	Molecular Weight	logP	Density	Water Solubility	Boiling Point	Melting Point
Tin Oxide	Gray tetragonal crystals	150.71	NA*	6.85 g/cm^3	Insoluble	NA	1630°C
Tin	Cubic crystals (gray tin); silvery tetragonal crystals (white tin)	118.71	NA	7.287 g/cm^3 (white tin); 5.769 g/cm^3 (gray tin)	Insoluble	2602°C (gray and white tin)	231.93°C (white tin); gray tin transition to white tin at 13.2°C

*NA = Not Available

Table 2. Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2011[10,11]

	Tin Oxide		
	# of Uses	Conc. (%)	
Exposure Type			
Eye Area	223	0.003 to 5	
Incidental Ingestion	342	0.008 to 1	
Incidental Inhalation-sprays	15	0.0005 to 0.08	
Incidental Inhalation-powders	42	0.0005 to 1	
Dermal Contact	472	0.000003 to 5	
Deodorant (underarm)	NR	NR	
Hair - Non-Coloring	9	0.0008 to 0.4	
Hair-Coloring	NR	0.04	
Nail	45	0.002 to 1	
Mucous Membrane	376	0.0005 to 1	
Baby Products	NR	NR	
Duration of Use			
Leave-On	833	0.000003 to 5	
Rinse off	38	0.0003 to 1	
Diluted for (bath) use	1	NR	
Totals*/Conc. Range**	872	0.000003 to 5	

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses

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

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