Safety Assessment of Zinc Salts as Used in Cosmetics

Status:	Scientific Literature Review for Public Comment
Release Date:	October 12, 2017
Panel Meeting Date:	December 4-5, 2017

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date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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.

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INTRODUCTION

This assessment reviews the safety of the following 28 inorganic and organometallic zinc salts as used in cosmetic formulations:

Zinc Acetate
Zinc Ascorbate
Zinc Ascorbate Hydroxide
Zinc Aspartate
Zinc Carbonate
Zinc Carbonate Hydroxide
Zinc Chloride
Zinc Chloride Hydroxide
Zinc Citrate
Zinc Cysteinate
Zinc Gluconate
Zinc Glutamate
Zinc Glycinate
Zinc Hexametaphosphate
Zinc Hydroxide
Zinc Lactate
Zinc Laurate
Zinc Myristate
Zinc Neodecanoate
Zinc Nitrate
Zinc Palmitate
Zinc Phosphate
Zinc Ricinoleate
Zinc Salicylate
Zinc Stearate
Zinc Sulfate
Zinc Sulfide
Zinc Undecylenate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*), most of the ingredients reviewed in this safety assessment have several functions in cosmetics; possible functions in cosmetics include hair conditioning agents, skin conditioning agents, cosmetic astringents, cosmetic biocides, preservatives, oral care agents, buffering agents, bulking agents, chelating agents, and viscosity increasing agents non-aqueous (Table 1).[1] However, there is no function reported for Zinc Sulfide.

The following zinc salts have been reviewed previously by the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) and determined to be safe for use in cosmetic products according to the use concentrations and practices specified in their respective safety assessment reports: Zinc Acetate (2012),[2] Zinc Citrate (2014),[3] Zinc Myristate (2010),[4] Zinc Ricinoleate (2007),[5] and Zinc Stearate (2002).[6,7] Excerpts from the summaries of the reports on the previously reviewed ingredients (as provided in those reports) are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (This information is not included in the tables or the summary section.) For complete and detailed information, please refer to the original documents, which are available on the CIR website (http://www.cir-safety.org/ingredients).

Some of the constituent acids or salts, related to the zinc salts in this report, have been reviewed previously by the Panel; a summary of safety conclusions for those ingredients is included in this report (Table 2). Those original reports are also available on the CIR website.

There are numerous studies available in the open literature on many of the zinc salts included in this safety assessment; therefore, this report contains a representative amount of data relevant to cosmetic safety. Because several of these ingredients, i.e. Zinc Chloride, Zinc Gluconate, Zinc Stearate, and Zinc Sulfate, are generally recognized as safe (GRAS) when used with good manufacturing practices as nutrients for human consumption (21CFR182.8985, 21CFR182.8988, 21CFR182.8994, 21CFR182.8997), the daily exposure from that food use is expected to result in a much larger systemic dose than that resulting from use in cosmetic products. Therefore, for GRAS ingredients, the focus of this report is on data other than oral toxicity and bioavailability (e.g., dermal exposure and irritation and sensitization endpoints).

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

Some of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website[8-22]. In this safety assessment, ECHA is cited as the reference for summaries of information obtained from the ECHA website. Also referenced in this safety assessment are summary data found in reports made publically available by the World Health Organization (WHO)[23-25] and the United States (U.S.) Food and Drug Administration (FDA).[26-36]

CHEMISTRY

Definition and Structure

The ingredients presented in this report are zinc salts, specifically of the $^{2+}$ (II) oxidation state cation of zinc. Both the inorganic and organometallic salts included in this assessment have a zinc cation in common (Figure 1).

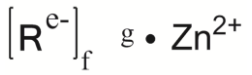


Figure 1. Zinc salts, wherein R is an anion and e*f = g*2

An example structure of Zinc Citrate is provided below (Figure 2).

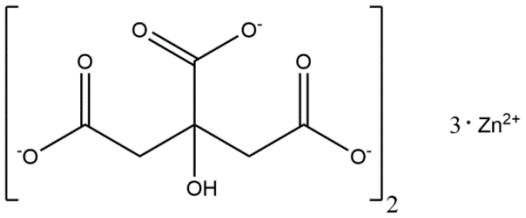


Figure 2. Zinc Citrate, an example salt (wherein R is citrate, e is 3 (1 for each "O^-"), f is 2, and g is 3)

Physical and Chemical Properties

Many of the zinc salts presented in this report are white or colorless crystalline solids, granules, or powders (Table 3). Formula weights range from 97 mg/mol (Zinc Sulfide) to 660 g/mol (Zinc Ricinoleate). Available melting point data reported relatively high (100-1700°C) values, with the exception of Zinc Nitrate (hexahydrate) that has a melting point of ~36°C. Zinc Acetate (dihydrate), Zinc Carbonate, Zinc Chloride, Zinc Citrate (dihydrate), Zinc Gluconate, Zinc Lactate (trihydrate), Zinc Nitrate (hexahydrate), Zinc Salicylate, and Zinc Sulfate (mono- and heptahydrate) are soluble in water. Zinc Phosphate is insoluble in water and alcohol, but soluble in dilute mineral acids, acetic acid, ammonia, and in alkali hydroxide solutions. Zinc Stearate and Zinc Sulfide are also insoluble in water. Zinc Stearate is soluble in benzene, but insoluble in alcohol and ether; Zinc Sulfide is insoluble in alkali metals, but soluble in dilute mineral acids.

In an animal feed application, the mean dusting potential (mass of the particles per cubic meter drawn from a rotating drum containing the test material)[37] of Zinc Chloride Hydroxide in 3 batches tested was < 0.025 g/m^3.[38] In five batches tested, the mean particle size distribution of Zinc Chloride Hydroxide was determined by laser diffraction to be 257-283 µm (none < 100 µm).

Method of Manufacture

Methods of manufacture of zinc salts are described in Table 4.[38-48]

Impurities

Zinc Acetate

According to the *Food Chemicals Codex (FCC)*, food grade specifications limit impurities in Zinc Acetate as follows: ≤ 3 mg/kg arsenic, ≤ 50 mg/kg chloride, ≤ 2 mg/kg lead, and ≤ 100 mg/kg sulfate.[49]

Zinc Carbonate

Zinc Carbonate contains cadmium as a minor constituent.[40]

Zinc Chloride

Potential impurities for Zinc Chloride include iron and manganese, however they can be removed by a precipitation reaction following neutralization with an alkali (i.e., zinc oxide) and oxidation with sodium hypochlorite (i.e., bleach) or chlorine.[41]

Zinc Gluconate

According to the *FCC*, food grade specifications limit impurities in Zinc Gluconate as follows: ≤ 2 mg/kg cadmium, ≤ 0.05% chloride, ≤ 2 mg/kg lead, and ≤ 0.05% sulfate.[49]

Zinc Stearate

According to the *FCC*, food grade specifications limit impurities in Zinc Stearate as follows: ≤ 10 mg (1.0%) residue weight of alkalies and alkaline earth metals, ≤ 1.5 mg/kg arsenic, ≤ 250 mg/kg chloride, ≤ 2 mg/kg lead, and ≤ 0.6% sulfate.[49] Zinc Stearate is typically a mixture of Zinc Stearate and Zinc Palmitate and may contain zinc oxide (13.5% to 15%).[43]

Zinc Sulfate

According to the *FCC*, food grade specifications limit impurities in Zinc Sulfate as follows: ≤ 5 mg (0.5%) residue weight of alkalies and alkaline earth metals, ≤ 2 mg/kg cadmium, ≤ 4 mg/kg lead, ≤ 5 mg/kg mercury, and ≤ 0.003% selenium.[49]

Zinc Sulfide

It has been reported that sulfides of Pb, Cd, Mn, and Cu may be present as impurities in Zinc Sulfide. Additionally, As, Sn, Bi, Co, Hg, In, Tl, Ga, Ge, Ag, and Au may be present in small quantities.[47]

Natural Occurrence

Generally, zinc is found in some seafood, red meats, and whole grains.[50] Human tissues and body fluids contain zinc. Human blood has been reported to contain zinc concentrations of 0.7 to 1.8 µg/ml.[51] In humans, most of the zinc is found in muscle and bones (~85%); total body zinc in men and women is approximately 2.5 and 1.5 g, respectively.[52] Smaller amounts of zinc are located in the skin and hair (~8%), liver (~5%), and gastrointestinal tract and pancreas (~3%).[25,53,54]

Zinc Carbonate

The naturally occurring minerals smithsonite and zincspar contain Zinc Carbonate.[43]

Zinc Carbonate Hydroxide

Zinc Carbonate Hydroxide occurs naturally as the mineral hydrozincite.[43]

Zinc Phosphate

Zinc Phosphate occurs naturally as the mineral hopeite.[43]

Zinc Sulfide

Zinc Sulfide occurs naturally as the minerals wurtzite and sphalerite.[43]

USE

Cosmetic

The Panel evaluates the safety of the cosmetic ingredients included in this assessment based on the expected use of and potential exposure to the ingredients in cosmetics. The data received from the U.S. FDA are collected from manufacturers through the FDA Voluntary Cosmetic Registration Program (VCRP), and include the use of individual ingredients in cosmetics by cosmetic product category. The data received from the cosmetic industry are collected by the Personal Care Products Council (Council) in response to a survey of the maximum reported use concentrations by product category. VCRP data obtained from the FDA in 2017[55] and Council survey data collected in 2016[56] indicate that 19 ingredients included in this safety assessment are used in cosmetic formulations.

According to 2017 VCRP data, Zinc Stearate, Zinc Gluconate, Zinc Sulfate, and Zinc Laurate have the highest number of reported uses at 2321, 318, 134, and 115 uses, respectively (Table 5).[55] Zinc Sulfate and zinc sulfate anhydrous were reported separately in the VCRP, but their uses have been combined in one table entry in this report (Table 5).[55] Concentration of use survey data (Table 5) indicated that the highest maximum reported concentrations of use were for Zinc Stearate (up to 32% in eye shadow) and Zinc Myristate (up to 20% in eye shadow and face powder).[56] The concentration of use survey data for Zinc Ascorbate Hydroxide is pending and will be added to the report when it becomes available.

Use concentration data were reported for Zinc Ascorbate, Zinc Glycinate, Zinc Phosphate, Zinc Salicylate, and Zinc Undecylenate, but no uses were received in the VCRP;[55,56] it should be presumed that there is at least one use in every category for which a concentration is reported. Conversely, VCRP data were reported for Zinc Acetate, Zinc Aspartate, and Zinc Hydroxide, but no use concentrations were reported in the Council survey. The ingredients not in use according to the VCRP and Council survey are listed in Table 6.

The 2017 frequency of use and 2016 concentration of use data for the 5 zinc salts in this safety assessment that have been reviewed previously are listed next to uses reported from their original safety assessments for comparison (Table 5).

Many of the zinc salts are reported to be used in cosmetic formulations indicative of potential eye exposure, possible mucous membrane exposure and/or ingestion. Zinc Ascorbate is used in baby shampoos (up to 0.01%)[56] and Zinc Stearate is reportedly used in baby lotions, oils, powders, and creams.[55]

The ingredients in this safety assessment are reportedly used in cosmetic sprays, including deodorant sprays and fragrances, and could possibly be inhaled. For example, Zinc Ascorbate is used in colognes and toilet waters up to 0.05% and Zinc Stearate is used in perfumes up to 0.3%.[56] Zinc Ricinoleate is used in deodorant aerosol (up to 2.3%) and pump sprays (up to 0.82%). 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 compared with pump sprays.[57-60] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[58,59] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in

the range considered to be respirable.[59] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Zinc Ascorbate, Zinc Chloride, Zinc Myristate, Zinc Stearate, Zinc Sulfate, and Zinc Undecylenate are reportedly used in face powders, dusting powders, or foot powders at concentrations between 0.02% to 20% and could possibly be inhaled.[56] The VCRP indicates that Zinc Laurate is reportedly used in face powders.[55] 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.[61-63]

According to Annex III/24 (i.e., "List of substances which cosmetic products must not contain except subject to the restrictions laid down"), the European Commission (EC) has restricted the following zinc salts to a maximum 1% zinc concentration in preparations ready for use: Zinc Acetate, Zinc Ascorbate, Zinc Ascorbate Hydroxide, Zinc Aspartate, Zinc Chloride, Zinc Citrate, Zinc Cysteinate, Zinc Gluconate, Zinc Glutamate, Zinc Glycinate, Zinc Lactate, Zinc Nitrate, Zinc Salicylate, and Zinc Sulfate.[64] According to Annex IV/150, Zinc Stearate is included on the "list of colorants allowed in cosmetic products."[65]

The German authority, Federal Institute for Risk Assessment (BfR), stated in 2014 that up to a maximum 10% of the upper intake level of zinc may be attributed to cosmetics.[54,67,68] BfR confirmed the safety for adults of up to 1% zinc in toothpastes, however for mouthwashes containing zinc up to 1% they were concerned that regular use over an extended period of time may contribute to exceeding the "10% share of UL (upper limit)" for zinc. The BfR was also concerned about children and adolescents being at a more susceptible risk because of their lower body weights. Therefore, BfR proposed that the maximum zinc concentration in oral hygiene products for adults not exceed 0.1% and that these products should not contain free zinc for people under the age of 18.

Cosmetics Europe conducted an aggregate exposure assessment, and in 2016 it was concluded that the food and oral care products combined exposures, including use of the allowed 1% zinc concentration in toothpastes, was safe for all age groups, and they supported a maximum concentration of up to 0.1% zinc in mouthwashes for all ages.[54]

The European Commission Scientific Committee on Consumer Safety (SCCS) published a preliminary report in 2017 on the SCCS opinion on water-soluble zinc salts used in oral hygiene products.[54] The SCCS concluded that exposure estimates to water-soluble zinc salts in toothpastes (1%) and mouthwashes (0.1%) could potentially result in daily intakes of 3.54 mg for adults and children (7-17 years). This would be 14% (adults) and 27% (children) of the recommended 25 mg/day upper limit for zinc; the SCCS considered these to be safe usages in oral hygiene products. In children up to 6 years of age, the SCCS estimated that water-soluble zinc salts exposure in toothpastes (1%) may result in daily intakes between 1.0 and 2.0 mg, which would be 10% and 29% of the recommended upper limit; the SCCS concluded that this would be a safe usage in toothpastes. The use of mouthwash is not recommended in children under 6 years of age. The SCCS also noted that it could not advise on the percentage of the zinc upper limit to attribute to cosmetic exposure. However, the SCCS did acknowledge that in children up to 17 years of age, depending on dietary exposure to zinc, it may be possible that aggregate zinc intake could exceed the upper limit.

Non-Cosmetic

The uses of many zinc salts, as specified in the Code of Federal Regulations (CFR) Title 21, are indirect food additives in packaging contacting food or as direct nutritional food additives intended for animal and human consumption (Table 7). In the U.S., Zinc Chloride, Zinc Gluconate, Zinc Stearate, and Zinc Sulfate are GRAS as direct food additive (nutritive) intended for human consumption when used with good manufacturing practice (21CFR182.8985, 21CFR182.8988, 21CFR182.8994, 21CFR182.8997).

The U.S. recommended dietary allowances (RDAs) for zinc are 11 mg/day and 8 mg/day for men and women, respectively.[70] It is recommended that pregnant and lactating women consume 12 mg zinc per day. The RDA for zinc in children 1-3 years, 4-8 years, 9-13 years, and 14-18 years are 3 mg/day, 5 mg/day, 8 mg/day, and 9-11 mg/day, respectively.

The EC Scientific Committee on Food (SCF) estimated that the tolerable upper intake level of zinc for children and adolescents was variable depending on surface area and body weight and ranged from 7 to 22 mg/day.[66] In 2003, the EC SCF issued an opinion in 2003 declaring that the tolerable upper intake level of zinc was recommended to be 25 mg/day for adults, including pregnant and lactating women. The following zinc salts may be used for nutritional purposes in the manufacture of foods and food supplements according to European legislation: Zinc Acetate, Zinc Chloride, Zinc Citrate, Zinc Gluconate, Zinc Lactate, Zinc Oxide, Zinc Carbonate, and Zinc Sulfate.

In the U.S., GRAS status was established for Zinc Acetate, Zinc Carbonate, Zinc Chloride, Zinc Gluconate, Zinc Stearate, and Zinc Sulfate with the use of good manufacturing and feeding practices in animals (21CFR582.80, 21CFR582.5985, 21CFR582.5988, 21CFR582.5994, 21CFR582.5997). In an European Food Safety Authority (EFSA) journal, the Panel on Additives and Products or Substances used in Animal Feed determined that Zinc Chloride Hydroxide (84% minimum Zinc Chloride Hydroxide (monohydrate), 54% minimum zinc content, 9% maximum zinc oxide, 2% maximum moisture, 5% maximum starch) would be safe to use as a zinc source in animal feed.[38]

Zinc Acetate (25 mg) is used in an oral capsule prescription drug product approved by the FDA.[26] Zinc Chloride (1 mg zinc/ml equivalent) is used in an injectable prescription drug product approved by the FDA.[27] The World Health Organization (WHO) lists Zinc Sulfate (20 mg solid form) as an oral administration drug used to treat diarrhea in children.[24]

According to the Title 21 of the CFR, there was inadequate safety data to establish safety and effectiveness in various over-the-counter (OTC) drug products for Zinc Acetate, Zinc Carbonate, Zinc Chloride, Zinc Stearate, Zinc Sulfide, and Zinc Sulfate (Table 7). The following zinc salts are FDA approved for use in other OTC drug products: Zinc Acetate, Zinc Carbonate, Zinc Sulfate, and Zinc Undecylenate (Table 7). Zinc Acetate, in skin protectants in OTC drug products for human use, and Zinc Stearate, in dusting powders in OTC drug products for human use, have Title 21 CFR labeling stipulations with cautionary statements; Zinc Stearate has occupational air contaminant limitations according to Title 29 of the CFR (Table 7).

Zinc Acetate is reported to be used as an inactive ingredient in various FDA approved drug products administered by subcutaneous (0.23% powder for injection suspension) or topical (concentration not specified) routes.[28] Zinc Carbonate is used as an inactive ingredient in an FDA approved drug product to be delivered subcutaneously (0.16% powder for injection suspension).[29] Zinc Chloride is listed as an inactive ingredient in FDA approved drug products to be administered orally (7 mg), subcutaneously (0.006%), intradermally (0.7%), or in ophthalmic solutions (0.003% w/v).[30] Zinc Stearate is used as an inactive ingredient in FDA approved drug products administered orally (2.04 mg to 36 mg) and dermally (6% in an emulsion cream).[31] Zinc Sulfate is used as an inactive ingredient in FDA approved drug products for oral administration (3.5 mg in a tablet).[32]

Zinc Acetate is listed as an ingredient in a wound dressing approved by the FDA as a legally marketed predicate medical device.[34] Zinc Chloride (concentration not specified) has been reported to be used in a wound cream[33] and wound cleanser[35] and Zinc Gluconate (0.02%) was listed as an active ingredient (breath freshener) in a mouthwash[36] that were approved by the FDA for 510(k) premarket notification to market a medical device substantially equivalent to other similar devices already legally marketed. Zinc Chloride has been reported to be used to desensitize teeth.[69]

TOXICOKINETIC STUDIES

Dermal Penetration

Provided below is a summary of dermal penetration data that are presented in detail in Table 8.

In an in vitro study in which Zinc Sulfate was applied to pig skin for 8 h without occlusion, zinc absorption was potentially 1.6%; 0.3% zinc was recovered in the receptor fluid, and 1.3% zinc was recovered in the horny layer.[20] Topical administration of an oil saturated with Zinc Chloride to pregnant Sprague-Dawley rats that were fed a zinc-deficient diet for 24 h resulted in plasma zinc levels similar to (8 h application) or greater than (following 24-h application) the plasma zinc levels of rats fed an adequate zinc diet.[71] In guinea pigs, <1% to 3.9% of 0.005 - 45.87M[^{65}Zn]-Zinc Chloride was absorbed in 5 h.[72] In rabbits, application of labeled Zinc Sulfate and Zinc Undecylenate demonstrated that the major mode of [^{65}Zn] uptake in skin is by diffusion through the hair follicles; there were no significant differences in the amount or location of [^{65}Zn] in skin treated with either compound.[48]

Absorption, Distribution, Metabolism, Excretion (ADME)

In vertebrates, zinc is involved in neurotransmission, cell signaling, and immune response, as well as, the metabolism of lipids, carbohydrates, proteins, and nucleic acids.[38] Zinc contributes to catalytic activity or the tertiary structure of proteins. In humans, depending on the amount of zinc ingested, approximately 70-80% of zinc is excreted in feces; urine, saliva, hair, breast milk, and sweat are other routes of elimination.[53,54] Zinc can be reabsorbed from the small intestines.

ADME studies are summarized below and detailed in Table 9.

In dermal studies, the penetration of [^{65}Zn] from various zinc chloride solutions in intact skin of rats resulted in the rapid appearance of [^{65}Zn] in the blood and other tissues; the maximum [^{65}Zn] activity in serum occurred within or around the first hour after application and was almost completely independent of the zinc concentration applied and the pH.[73]

In oral studies, plasma, urinary, and blood zinc levels increased in dogs with increasing doses of Zinc Acetate.[74] In Sprague-Dawley rats given Zinc Carbonate in the diet, the study authors suggested that absorptive capacity of zinc is adaptive and greater in groups deficient or marginally deficient in zinc.[75] In rats fed radiolabeled Zinc Carbonate, Zinc Chloride, and Zinc Chloride Hydroxide, the percent absorption of ^{65}Zn was similar with all three substances, ranging from 40-48%.[42] In a study examining the distribution of zinc to different organs after a single oral administration of Zinc Chloride in rats, it was determined that zinc was mainly accumulated in small intestine, liver, kidneys and large intestine.[8] In human subjects that were given a single oral dose of 50 mg elemental zinc as the acetate salt under either high (pH > 5) or low (pH < 3) intragastric pH conditions, absorption was faster with low intragastric pH. [13]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute toxicity studies summarized below are presented in Table 10.

The dermal LD_{50}s of Zinc Stearate (in rabbits),[53] Zinc Sulfate (in rats),[8,14,20] and Zinc Sulfide (in rats)[76] are >2000 mg/kg. Reported oral LD_{50}s are 287 mg/kg Zinc Acetate (dihydrate) in mice,[77] 794 mg/kg Zinc Acetate (dihydrate) is in rats,[77] between 500 mg/kg and 2000 mg/kg Zinc Lactate in rats,[14] 926 mg/kg Zinc Nitrate (hexahydrate) in mice,[77] 1330 mg/kg Zinc Nitrate (hexahydrate) in

rats,[77] > 5000 mg/kg Zinc Phosphate in rats,[11] > 2000 mg/kg Zinc Ricinoleate in rats,[15] and > 5000 mg/kg Zinc Stearate in rats.[53] In inhalation studies, reported LC_{50}s are 2000 mg/m^3 Zinc Chloride in rats[14] and > 200,000 mg/m^3 Zinc Stearate in rats.[53] In dogs and sheep, inhalation exposure to ≤ 5.18mg/m^3 (1%) and ≤ 8.3 mg/m^3 (0.5%) Zinc Sulfate, respectively, for up to 4 h did not affect lung function (dogs) or tracheal mucous velocity (sheep).[78]

Subchronic Toxicity Studies

Subchronic toxicity studies summarized below are presented below are presented in Table 11.

In a 3-mo study in which 160 – 640 mg/kg/day Zinc Acetate (dihydrate) was added to drinking water of rats, a no-observed-effect-level (NOEL) of 160 mg/kg/day was reported; concentrations of zinc were statistically significantly higher in several organs and the blood of animals of the mid- and high-dose groups.[13,79] In a 13-wk feed study of Zinc Sulfate, a NOEL of 3000 ppm was reported in mice and rats; some mice (but no rats) dosed with 30,000 ppm died, and numerous toxic effects were reported in both mice and rats of the 30,000 ppm groups.[10,80] No significant toxicologic effects or pulmonary or cardiac changes were reported in an inhalation study in rats exposed to 100 µg/m^3 water soluble Zinc Sulfate for 5 h/day for 3 days/week for 16 wks.[81] In a study in which human subjects were given a supplement with 15 or 100 mg/day zinc, supplied as Zinc Acetate, for 3 mos, plasma zinc concentrations were statistically significantly higher in 100 mg/day group, but not in the 15 mg/day group; other blood chemistries were not affected.[82]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Provided below is a summary of DART studies that are presented in detail in Table 12.

Mice were given 500 or 1000 mg/l Zinc Acetate in the drinking water from mating through weaning; a lowest-observable-adverse-effect-level (LOAEL) of 136 mg/kg/day zinc in male and female mice was reported due to an increase in direct plaque-forming activity of spleen cells and an increase in lymphocyte proliferation with mitogen stimulation.[13] In rats dosed by gavage with up to 30 mg/kg/day aq. Zinc Chloride for 84 days (premating through lactation), adverse effects were reported in the dams and the offspring, including a reduced number of live pups/litter, a decreased live birth index, increased mortality, and increased fetal resorption.[83] In a two-generation reproduction toxicity study in which rats were dosed with up to 30 mg/kg/day aq. Zinc Chloride, the overall no-observed-adverse-effect-level (NOAEL) was 7.5 mg/kg/day for the F_1 generation.[14,84] Parental animals from F_0 and F_1 generations showed reduced fertility and viability, and effects on organ weights were reported in parental animals; reduced body weights were reported for F_1 and F_2 pups in 30 mg/kg/day group, however no effects on weaning index, sex ratio, or litter size observed. The developmental and reproductive effects of Zinc Sulfate was examined in mice (≤ 30 mg/kg/day),[10] rats (up to 42.5 mg/kg)[85], hamsters (≤ 88 mg/kg/day),[9,20] and rabbits (≤ 60 mg/kg);[85] no developmental effects were observed. In studies in which male rats were fed a diet containing 4000 ppm zinc as Zinc Sulfate,[10,86] there was a decrease in the conception rate, and a statistically significantly lower number of live births per mated female. In a study in which female rats were fed a diet containing 4000 ppm zinc as Zinc Sulfate, a decrease in the conception rate was reported when the animals were dosed from the first day of conception through study termination, but not in the group that were dosed 21-26 days prior to dosing, through day 18 of gestation; there were no other statistically significant effects on reproductive parameters.[87]

GENOTOXICITY

Provided below is a summary of genotoxicity studies that are presented in detail in Table 13.

Positive and negative results were found in genotoxicity studies of zinc salts. In in vitro studies, Zinc Acetate was negative in an Ames test (≤ 7200 µg/plate),[88] unscheduled DNA synthesis (UDS) assay in rat hepatocytes (≤ 1000 µg/ml), and in human lymphocytes,[89] but it was positive in a mouse lymphoma assay in a dose-dependent manner (1.3 - 13 µg/ml without and 4.2 - 42 µg/ml with metabolic activation)[88] and in a chromosomal aberration assay in Chinese hamster ovary (CHO) cells (25 - 45 µg/ml without and 45 - 80 µg/ml with metabolic activation). Zinc Chloride was not mutagenic in an Ames test (≤ 100 mg/l),[90] a mouse lymphoma assay (≤ 12.13 µg/ml),[91] or chromosomal aberration assay in human dental pulp cells (≤ 300 µM);[69] it was genotoxic in a clastogenicity study in human peripheral blood leucocytes [92] and in a micronucleus assay with human peripheral blood lymphocytes (at 100 mg/l),[90] it was positive in a cytokinesis-block micronucleus assay,[93] and 3.2 mM caused a 2-fold increase in λ-prophage induction in *Escherichia coli* WP2 as compared to controls.[14] Zinc Nitrate ≤ 1 mM),[94] Zinc Stearate (concentrations not specified),[16] and Zinc Sulfate (≤ 3600 µg/plate)[10] were not mutagenic in the Ames test, and Zinc Sulfate was non-convertogenic in a mitotic recombination assay performed with 4-h exposure duration in *Saccharomyes cerevisiae* diploid strain D4.[17] Zinc Chloride was genotoxic in several in vivo assays using mice; statistically significant, dose-dependent increases were observed in chromosomal aberrations of bone-marrow cells (≤ 15 mg/kg),[95] in sperm-head abnormalities (≤ 15 mg/kg), and in a Comet assay (eukaryotic cells; ≤ 19.95 mg/kg).[96]

CARCINOGENICITY

Animal

Chester Beatty mice were administered Zinc Sulfate (heptahydrate; 1000 ppm and 5000 ppm) in their drinking water for 45 to 53 weeks. Controls were used, however some died due to a viral infection and were, therefore, replaced with additional control animals (no further details).[53] Results indicated that occurrences of hepatoma, malignant lymphoma, lung adenoma, and evidence of hyperplasia in the forestomach epithelium were not higher in treated animals compared to control animals. There were no other tumors observed.

OTHER RELEVANT STUDIES

Transformation

In Vitro

Zinc Chloride

A transformation assay was performed using cells from Syrian hamster embryos (cryopreserved at day 14 of gestation).[97] Zinc Chloride was evaluated to determine whether it produced a morphological transformation effect on the hamster embryo cells. Twenty-four hours after target cells (up to 250) were seeded in appropriate medium, Zinc Chloride (22 µM) was added to the cell culture. Colonies from these cell cultures were prepared for counting 8 to 9 days following seeding of the target cells. A similar experiment was conducted with a known carcinogenic promoter, benzo(*a*)pyrene (3.2 µM), in cell cultures both with and without the addition of Zinc Chloride. Control cell cultures to which neither Zinc Chloride nor benzo(*a*)pyrene were added or only benzo(*a*)pyrene was added were also examined. The transformation frequencies reported were 0%, 0.7%, 0%, and 0.4% for control (without Zinc Chloride or benzo(*a*)pyrene), benzo(*a*)pyrene only, Zinc Chloride only, and Zinc Chloride plus benzo(*a*)pyrene, respectively. The study researchers concluded that Zinc Chloride did not induce transformation on its own or enhance transformation when benzo(*a*)pyrene was present.

Another transformation assay conducted in Syrian hamster embryo cells (13 to 14 days into gestation) showed that Zinc Chloride (up to 20 µg/ml of appropriate medium) did not induce morphological transformation after cells were exposed to the test substance for 7 to 8 days; Zinc Chloride was reported to reduce the cloning efficiency by 20 to 25%.[98] Both negative and positive (benzo(*a*)-pyrene) controls were used and performed as expected.

Cytotoxicity

In Vitro

Zinc Gluconate

Tests were conducted in human nasal explants exposed to Zinc Gluconate in a tradename product marketed for cold symptoms to evaluate cytotoxicity; the Zinc Gluconate concentration in the tradename product not specified.[99] The treated nasal tissues showed statistically significantly elevated lactate dehydrogenase levels compared to controls (saline-treated); treated tissues were confirmed by histology to have severe necrosis. These results indicated that the tradename product caused substantial cytotoxicity. Around the time of this study the FDA issued a public health advisory against using some of the nasal products containing this tradename ingredient because of the risk of anosmia.

Zinc Sulfate

An in vitro screening assay in serum-free culture medium was conducted to determine if intranasal Zinc Sulfate (0.01%, 0.1%, 1%, 5%) and a tradename product nasal spray used for cold symptoms were cytotoxic to human sinonasal explant tissues.[100] Negative controls (0.9% saline and distilled water) were used. Extracellular lactate dehydrogenase levels were measured and histopathology performed on the explants to determine their biochemical properties. Zinc Sulfate at 1% and 5% and the tradename product were found to be highly cytotoxic compared to controls.

In Vivo

Zinc Gluconate

Experiments performed in C57BL/6 mice showed that intranasal administration of 15 µl of a tradename product (concentration of Zinc Gluconate in the product not specified) into both cavities was highly cytotoxic to nasal tissues.[99] Olfactory sensory neurons were damaged in treated mice that cold not detect odorants during behavioral testing approximately 1 week post-treatment; by 2 months post-treatment there was no recovery of function. Saline controls performed as expected; differences in results between treated and control mice were statistically significant. Further tests revealed atrophy of main olfactory epithelium observed in treated tissues; a reduction in biochemical markers of the main olfactory epithelium (adenylyl cyclase 3, β-tubulin, and olfactory marker protein) was seen in treated samples.

Effect on Hypopigmentation

In Vivo

Zinc Sulfate

The effects of Zinc Sulfate on murine hair follicle melanogenesis were evaluated in an oral exposure experiment.[101] C57BL/6a/a mice were administered up to 20 mg/ml (~1200 mg/kg) Zinc Sulfate (heptahydrate) in their drinking water daily for 4 days prior to depilation or spontaneous anagen induction and up to 28 days to 1 year during hair follicle cycling. Unadulterated drinking water was administered to control animals. Hair pigmentation was evaluated using electron paramagnetic resonance (EPR) to detect melanin. There was a 10% drop in body weight in treated animals, but it reversed after 2 weeks and was thought by study researchers to be caused by decreased water intake. During spontaneous and depilation-induced hair growth cycles it was noted that hair pigmentation turned from the normal black to a bright brown in treated animals, which was not observed in controls. This was correlated with dose-dependency, but not attributed to a change in quality of melanin. Pigment generation was not transferred from eumelanogenesis to phaeomelanogenesis. EPR testing showed that Zinc Sulfate treatment inhibited anagen-coupled eumelanogenesis. After completion of a full hair cycle, skin and hair shaft melanin content was statistically significantly reduced in treated compared to control animals; hair shaft depigmentation was observed during multiple hair cycles in treated animals.

Corneal Wound Healing

In Vivo

Zinc Chloride

The effects of Zinc Chloride on corneal wound healing were evaluated in male Wistar rats with corneal abrasion.[102] One drop (~40 µl) of the Zinc Chloride solution (pH 7.0) at concentrations of 0.0010%, 0.0025%, or 0.0050% was instilled into the eyes of rats 5 times per day. Saline controls were similarly prepared. Rats were anesthetized and 12 mm^2 samples of the corneas were removed, dyed and digitally analyzed to determine the extent of corneal wound healing up to 36 hours after corneal epithelial abrasion occurred. Corneal wound healing improved with decreasing concentrations of Zinc Chloride. Notably by 24 hours following corneal abrasion, the 0.0010% and 0.0025% concentrations showed statistically significant improvement of > 90% corneal wound healing compared to the saline control samples which showed 83% healing, based on the means of 4 to 11 rat corneas.

DERMAL IRRITATION AND SENSITIZATION STUDIES

A summary of dermal irritation and sensitization studies is provided below, and details are presented in Table 14.

In a 5-day open patch study, Zinc Acetate (20% in deionized water) was irritating in mouse skin, non-irritating in guinea pig, and slightly irritating in rabbit skin, Zinc Chloride (1% in deionized water) was severely irritating in mouse and rabbit skin and irritating in guinea pig skin, Zinc Sulfate (1% in deionized water) was slightly irritating in all three species, and Zinc Undecylenate (20% in 0.1% Tween 80 vehicle) was slightly irritating in mouse and rabbit skin and non-irritating in guinea pig skin.[103] The test substances were also evaluated in a closed patch test in rabbits that included a 3-day patch followed by a 2-day patch; Zinc Acetate and Zinc Chloride were severely irritating and Zinc Sulfate and Zinc Undecylenate were slightly irritating. Four h patches of Zinc Lactate (occlusive),[14] Zinc Neodecanoate (semi-occlusive),[18] Zinc Ricinoleate (occlusive),[15] and Zinc Sulfate (semi-occlusive) [20] were non-irritating to rabbit skin; the test materials were applied undiluted. A single application of Zinc Nitrate resulted in pronounced skin irritation in rats, rabbits, and guinea pigs; details were not provided.[22] In clinical testing, Zinc Sulfide[21] and two eye shadows containing 10% Zinc Stearate[53] were non-irritating; details not provided.

In a mouse local lymph node assay, a 10% solution of Zinc Sulfate was non-sensitizing.[14,104] In a guinea pig maximization test of Zinc Sulfate (0.1% for intradermal induction; 50% for epidermal induction and challenge), weak reactions were reported in 5/10 treated animals and 2/5 control animals; following a second challenge, reactions noted in 4/10 treated animals and 2/5 controls.[53] An eye shadow containing 10% Zinc Stearate was non-sensitizing in Schwartz-Speck prospective patch test or in a human repeated insult patch test.[53]

OCULAR IRRITATION

Zinc Chloride in a water solution or as a solid is an astringent and may cause potential eye irritation.[105]

The ocular irritation studies that are summarized below are presented in Table 15.

In in vitro studies, Zinc Acetate (97%) was corrosive in an isolated chicken eye test,[13] and Zinc Citrate was considered an irritant in a reconstructed human cornea-like epithelium test.[12] In rabbit eyes, Zinc Phosphate[11] and Zinc Ricinoleate[15] were non-irritating, Zinc Nitrate was irritating,[22] Zinc Lactate was very irritating,[14] and Zinc Sulfate was severely irritating.[19,20]

CLINICAL STUDIES

Retrospective and Multicenter Studies

In a Health Professionals Follow-Up Study, researchers evaluated the association of supplemental zinc consumption and risk of prostate cancer in 46,974 men in the United States.[106] In the 14 years (1986 - 2000) of follow-up, there were 2901 new cases of prostate cancer. Of the new cases, 434 were advanced cancer. Study researchers observed that there was no association with prostate cancer risk in those who consumed supplements of 100 mg zinc (usually in the form of Zinc Gluconate) or less per day. Compared to men who did not consume zinc supplements, those who supplemented with more than 100 mg/day zinc showed a 2.29 (95% confidence interval of 1.06 to 4.95, p = 0.003) relative risk in advanced prostate cancer. The risk increased to 2.37 (95% confidence interval of 1.42 to 3.95, p = 0.001) for men who supplemented with zinc for 10 years or more. The study researchers noted that there could be confounding factors such as calcium intake supplementation or another unmeasured correlation related to zinc supplementation, but that the potential for long-term zinc supplementation to contribute to prostate carcinogenesis should be further investigated.

Inhalation Exposure

Zinc Chloride

In humans, inhalation exposure via aerosol (exposure duration not specified) to 40 mg/m^3 Zinc Chloride (19.2 mg/m^3 zinc) produced a metallic taste; the particle size and other details were not provided.[53] Another study reported that in human subjects exposed via inhalation to 4800 mg/m^3 Zinc Chloride for 30 minutes, pulmonary effects were induced (no further details).

Clinical Reports

Administration of Zinc Acetate, Zinc Citrate, and Zinc Sulfate did not have adverse effects in pregnant women; beneficial effects were observed in some,[107-109] but not all,[110] of the studies. (Table 16)

Case Reports

Inhalation

Zinc Chloride

There are case reports involving slowly progressing adult respiratory distress syndrome (~10 to 32 days post-exposure),[111] sometimes resulting in death, after inhalation of Zinc Chloride from a smoke bomb.[111-118] In a case where a patient survived, corticosteroid treatment and extracorporeal life support measures were followed.[112]

There is a report of a patient who permanently lost all sense of smell after splashing a Zinc Chloride solution into his nasal passages (no further details provided).[53]

Oral

Zinc Chloride

A male patient had a 1-yr history of multiple pruritic eruptions over his whole body; the erythematous, edematous lesions were 3 to 10 mm in diameter and were resistant to treatment with topical corticosteroids and antihistamines.[119] The patient had dental fillings installed 3 mos prior to the onset of the rash. A metal series patch test, which included 2% Zinc Chloride, and histology were performed. Positive reaction were observed for Zinc Chloride on days 2 through 7 following patch testing; the patient tested negative for 12 other dental allergens. Skin lesions from previous sites worsened substantially during patch testing. The concentration of zinc in the serum was normal (eosinophilia was noted). A stimulation index of 518% (< 180% is normal) was reported for Zinc Chloride during a lymphocyte stimulation test. A biopsy of erythematous lesion of the back reported spongiosis and perivascular lymphocytic infiltration. The patient was diagnosed with systemic allergic dermatitis caused by zinc. Severe reactions were reported during removal of the fillings, and corticosteroids were needed. Following removal of dental fillings, the patient's skin reactions improved. The study researchers speculated that the Zinc Chloride in the dental materials was absorbed through oral mucosa or skin, based on this case report. They also noted that zinc absorbed through diet is likely greater than that absorbed from a dental filling.

There are case reports in the literature of poisonings following oral ingestion of large amounts of Zinc Chloride in adults[120-122] and children.[123-126] Symptoms reported in adults included corrosive gastroenteritis, vomiting, abdominal pain, and diarrhea; fatalities have been reported with cause of death in one case assigned to severe metabolic acidosis resulting from organ damage caused by zinc chloride poisoning (patient's blood zinc concentration on arrival to hospital was 3030 µg/dl).[120] Hypotension and liver cirrhosis were observed in this case, but there was no gastrointestinal perforation; zinc content was highest in the gastric mucosa, pancreas, and spleen. In children, reported symptoms of Zinc Chloride poisoning included symptoms of corrosive pharyngeal lesions, vomiting, lethargy, metabolic acidosis, gastric corrosion, and liver damage.[123-125] A 10-year-old girl developed an antral stricture in her stomach 3 weeks following accidental ingestion of a soldering flux solution containing Zinc Chloride (30% to < 60%) and underwent Heineke-Mikulicz antropyloroplasty with an uneventful recovery, although on follow-up delayed gastric

emptying was noted.[124] Chelation therapy in children and adults was initiated if systemic toxicity persisted or when serum zinc levels were elevated.[122,123,125,126]

Zinc Sulfate

There was a case report of a 16-year-old boy who overdosed on Zinc Sulfate tablets; spontaneous and induced emesis and orogastric lavage occurred, followed by whole-bowel irrigation.[127] The patient's serum chloride increased, but the zinc tablets cleared the gastrointestinal tract after an additional 24 hours.

Ocular

Zinc Chloride

A concentrated solution of Zinc Chloride was inadvertently splattered into two patients' eyes. Corneal edema and scarring were observed; visual acuity became optimal after 6 to 28 weeks.[53]

Occupational Exposure

In a World Health Organization report, there is mention of rubber workers exposed to Zinc Stearate who have experienced dermal irritation (no further details provided).[23]

SUMMARY

This report addresses the safety of 28 inorganic and organometallic zinc salts as used in cosmetic formulations. According to the wINCI *Dictionary*, these ingredients have many functions in cosmetics including hair conditioning agents, skin conditioning agents, cosmetic astringents, cosmetic biocides, preservatives, oral care agents, buffering agents, bulking agents, chelating agents, and viscosity increasing agents. The ingredients named in this assessment are all zinc salts, specifically of the $^{2+}$ (II) oxidation state cation of zinc.

VCRP data obtained from the U.S. FDA and data received in response to a survey of the maximum reported use concentration by product category conducted by the Council indicate that 20 of the 28 ingredients included in this safety assessment are used in cosmetic formulations. According to 2017 VCRP data, Zinc Stearate is reported to be used in 2321 formulations. According to the results of a concentration of use survey conducted in 2016, the highest maximum reported concentrations of use were for Zinc Stearate (up to 32% in eye shadow) and Zinc Myristate (up to 20% in eye shadow and face powder).

The European Commission restricts Zinc Acetate, Zinc Ascorbate, Zinc Ascorbate Hydroxide, Zinc Aspartate, Zinc Chloride, Zinc Citrate, Zinc Cysteinate, Zinc Gluconate, Zinc Glutamate, Zinc Glycinate, Zinc Lactate, Zinc Nitrate, Zinc Salicylate, and Zinc Sulfate to a maximum 1% zinc concentration in preparations ready for use. Additionally, Zinc Stearate is included on the list of colorants allowed in cosmetic products.

Many of the zinc salts are indirect food additives allowed in packaging that contacts food or are direct nutritional food additives intended for animal and human consumption. In the U.S., Zinc Chloride, Zinc Gluconate, Zinc Stearate, and Zinc Sulfate are GRAS as direct food additive (nutritive) intended for human consumption when used with good manufacturing practice. GRAS status (U.S.) was established for Zinc Acetate, Zinc Carbonate, Zinc Chloride, Zinc Gluconate, Zinc Stearate, and Zinc Sulfate with the use of good manufacturing and feeding practices in animals.

The U.S. recommended dietary allowances (RDAs) for zinc are 11 mg/day and 8 mg/day for men and women, respectively. It is recommended that pregnant and lactating women consume 12 mg zinc/day. The RDA for zinc in children 1-3 years, 4-8 years, 9-13 years, and 14-18 years are 3 mg/day, 5 mg/day, 8 mg/day, and 9-11 mg/day, respectively.

In an in vitro study in which Zinc Sulfate was applied to pig skin for 8 h without occlusion, zinc absorption was potentially 1.6%; 0.3% zinc was recovered in the receptor fluid, and 1.3% zinc was recovered in the horny layer. Topical administration of an oil saturated with Zinc Chloride to pregnant Sprague-Dawley rats that were fed a zinc-deficient diet for 24 h resulted in plasma zinc levels similar to (8 h application) or greater than (following 24-h application) the plasma zinc levels of rats fed an adequate zinc diet. In guinea pigs, <1% to 3.9% of 0.005 - 45.87M [^{65}Zn]-Zinc Chloride was absorbed in 5 h. In rabbits, application of labeled Zinc Sulfate and Zinc Undecylenate demonstrated that the major mode of [^{65}Zn] uptake in skin is by diffusion through the hair follicles; there were no significant differences in the amount or location of [^{65}Zn] in skin treated with either compound.

In vertebrates, zinc is involved in neurotransmission, cell signaling, and immune response, as well as, the metabolism of lipids, carbohydrates, proteins, and nucleic acids. Zinc contributes to catalytic activity or the tertiary structure of proteins. In humans, depending on the amount of zinc ingested, approximately 70-80% of zinc is excreted in feces; urine, saliva, hair, breast milk, and sweat are other routes of elimination. Zinc can be reabsorbed from the small intestines.

In dermal studies, the penetration of [^{65}Zn] from various zinc chloride solutions in intact skin of rats resulted in the rapid appearance of [^{65}Zn] in the blood and other tissues; the maximum [^{65}Zn] activity in serum occurred within or around the first hour after application and was almost completely independent of the zinc concentration applied and the pH. In oral studies, plasma, urinary, and blood zinc levels increased in dogs with increasing doses of Zinc Acetate. In Sprague-Dawley rats given Zinc Carbonate in

the diet, the study authors suggested that absorptive capacity of zinc is adaptive and greater in groups deficient or marginally deficient in zinc. In rats fed radiolabeled Zinc Carbonate, Zinc Chloride, and Zinc Chloride Hydroxide, the percent absorption of ^{65}Zn was similar with all three substances, ranging from 40-48%. In a study examining the distribution of zinc to different organs after a single oral administration of Zinc Chloride in rats, it was determined that zinc was mainly accumulated in small intestine, liver, kidneys and large intestine. In human subjects that were given a single oral dose of 50 mg elemental zinc as the acetate salt under either high (pH > 5) or low (pH < 3) intragastric pH conditions, absorption was faster with low intragastric pH.

The dermal LD_{50}s of Zinc Stearate (in rabbits), Zinc Sulfate (in rats), and Zinc Sulfide (in rats) are > 2000 mg/kg. Reported oral LD_{50}s are 287 mg/kg Zinc Acetate (dihydrate) in mice, 794 mg/kg Zinc Acetate (dihydrate) is in rats, between 500 mg/kg and 2000 mg/kg Zinc Lactate in rats, 926 mg/kg Zinc Nitrate (hexahydrate) in mice, 1330 mg/kg Zinc Nitrate (hexahydrate) in rats, > 5000 mg/kg Zinc Phosphate in rats, > 2000 mg/kg Zinc Ricinoleate in rats, and > 5000 mg/kg Zinc Stearate in rats. In inhalation studies, reported LC_{50}s are 2000 mg/m^3 Zinc Chloride in rats and > 200,000 mg/m^3 Zinc Stearate in rats. In dogs and sheep, inhalation exposure to ≤ 5.18mg/m^3 (1%) and ≤8.3 mg/m^3 (0.5%) Zinc Sulfate, respectively, for up to 4 h did not affect lung function (dogs) or tracheal mucous velocity (sheep).

In a 3-mo study in which 160 – 640 mg/kg/day Zinc Acetate (dihydrate) was added to drinking water of rats, a NOEL of 160 mg/kg/day was reported; concentrations of zinc were statistically significantly higher in several organs and the blood of animals of the 640 mg/kg/day groups. In a 13-wk feed study of Zinc Sulfate, a NOEL of 3000 ppm was reported in mice and rats; some mice (but no rats) dosed with 30,000 ppm died, and numerous toxic effects were reported in both mice and rats of the 30,000 ppm groups. No significant toxicologic effects or pulmonary or cardiac changes were reported in an inhalation study in rats exposed to 100 µg/m^3 water soluble Zinc Sulfate for 5 h/day for 3 days/week for 16 wks. In a study in which human subjects were given a supplement with 15 or 100 mg/day zinc, supplied as Zinc Acetate, for 3 mos, plasma zinc concentrations were statistically significantly higher in 100 mg/day group, but not in the 15 mg/day group; other blood chemistries were not affected.

Mice were given 500 or 1000 mg/l Zinc Acetate in the drinking water from mating through weaning; a LOAEL of 136 mg/kg/day zinc in male and female mice was reported due to an increase in direct plaque-forming activity of spleen cells and an increase in lymphocyte proliferation with mitogen stimulation. In rats dosed by gavage with up to 30 mg/kg/day aq. Zinc Chloride for 84 days (premating through lactation), adverse effects were reported in the dams and the offspring, including a reduced number of live pups/litter, a decreased live birth index, increased mortality, and increased fetal resorption. In a two-generation reproduction toxicity study in which rats were dosed with up to 30 mg/kg/day aq. Zinc Chloride, the overall NOAEL was 7.5 mg/kg/day for the F_1 generation. Parental animals from F_0 and F_1 generations showed reduced fertility and viability, and effects on organ weights were reported in parental animals; reduced body weights were reported for F_1 and F_2 pups in 30 mg/kg/day group, however no effects on weaning index, sex ratio, or litter size observed. The developmental and reproductive effects of Zinc Sulfate was examined in mice (≤30 mg/kg/day), rats (up to 42.5 mg/kg), hamsters (≤88 mg/kg/day), and rabbits (≤60 mg/kg); no developmental effects were observed. In studies in which male rats were fed a diet containing 4000 ppm zinc as Zinc Sulfate, there was a decrease in the conception rate, and a statistically significantly lower number of live births/mated female. In a study in which female rats were fed a diet containing 4000 ppm zinc as Zinc Sulfate, a decrease in the conception rate was reported when the animals were dosed from the first day of conception through study termination, but not in the group that were dosed 21-26 days prior to dosing, through day 18 of gestation; there were no other statistically significant effects on reproductive parameters.

Both positive and negative results were reported in genotoxicity studies of zinc salts. In in vitro studies, Zinc Acetate was negative in an Ames test (≤ 7200 µg/plate), UDS assay in rat hepatocytes (≤ 1000 µg/ml), and in human lymphocytes, but it was positive in a mouse lymphoma assay in a dose-dependent manner (1.3 - 13 µg/ml without and 4.2 - 42 µg/ml with metabolic activation) and in a chromosomal aberration assay in CHO cells (25 - 45 µg/ml without and 45 - 80 µg/ml with metabolic activation). Zinc Chloride was not mutagenic in an Ames test (≤ 100 mg/l), a mouse lymphoma assay (≤ 12.13 µg/ml), or chromosomal aberration assay in human dental pulp cells (≤ 300 µM); it was genotoxic in a clastogenicity study in human peripheral blood leucocytes and in a micronucleus assay with human peripheral blood lymphocytes (at 100 mg/l), in a cytokinesis-block micronucleus assay, and 3.2 mM caused 2-fold increase in λ-prophage induction in *Escherichia coli* WP2 as compared to controls. Zinc Nitrate ≤ 1 mM),[94] Zinc Stearate (concentrations not specified),[16] and Zinc Sulfate (≤3600 µg/plate)[10] were not mutagenic in the Ames test, and Zinc Sulfate was non-convertogenic in a mitotic recombination assay performed with 4-h exposure duration in *Saccharomyes cerevisiae* diploid strain D4. Zinc Chloride was genotoxic in several in vivo assays using mice; statistically significant, dose-dependent increases were observed in chromosomal aberrations of bone-marrow cells (≤ 15 mg/kg), in sperm-head abnormalities (≤ 15 mg/kg), and in a Comet assay (eukaryotes; ≤ 19.95 mg/kg).

Zinc Sulfate did not have carcinogenic effects Chester Beatty mice. Zinc Chloride did not induce transformation in Syrian hamster embryo cells either on its own or enhance transformation when benzo(*a*)pyrene was present.

Zinc Sulfate (at up to 5%) and Zinc Gluconate and Zinc Sulfate (at unspecified concentration in an OTC product) were very cytotoxic in human nasal explant tissues. The OTC product containing Zinc Gluconate was also cytotoxic and damaging to nasal tissues of mice.

Zinc Sulfate, administered in the drinking water of mice, resulted in a statistically significantly reduction in skin and hair shaft melanin content.

In a 5-day open patch study, Zinc Acetate (20% in deionized water) was irritating in mouse skin, non-irritating in guinea pig, and slightly irritating in rabbit skin, Zinc Chloride (1% in deionized water) was severely irritating in mouse and rabbit skin and irritating in guinea pig skin, Zinc Sulfate (1% in deionized water) was slightly irritating in all three species, and Zinc Undecylenate (20% in 0.1% Tween 80 vehicle) was slightly irritating in mouse and rabbit skin and non-irritating in guinea pig skin. The test substances were also evaluated in a closed patch test in rabbits that included a 3-day patch followed by a 2-day patch; Zinc Acetate and Zinc Chloride were severely irritating and Zinc Sulfate and Zinc Undecylenate were slightly irritating. Four h patches of Zinc Lactate (occlusive), Zinc Neodecanoate (semi-occlusive), Zinc Ricinoleate (occlusive), and Zinc Sulfate (semi-occlusive) were non-irritating to rabbit skin; the test materials were applied undiluted. A single application of Zinc Nitrate resulted in pronounced skin irritation in rats, rabbits, and guinea pigs; details were not provided. In clinical testing, Zinc Sulfide and two eye shadow formulations containing 10% Zinc Stearate were non-irritating; details not provided.

In a mouse local lymph node assay, a 10% solution of Zinc Sulfate was non-sensitizing. In a guinea pig maximization test of Zinc Sulfate (0.1% for intradermal induction; 50% for epidermal induction and challenge), weak reactions were reported in 5 of 10 treated animals and 2 of 5 control animals; following a second challenge, reactions noted in 4 of 10 treated animals and 2 of 5 controls. An eye shadow containing 10% Zinc Stearate was non-sensitizing in Schwartz-Speck prospective patch test and in a human repeated insult patch test.

In in vitro studies, Zinc Acetate (97%) was corrosive in an isolated chicken eye test, and Zinc Citrate was considered an irritant in a reconstructed human cornea-like epithelium test. In rabbit eyes, Zinc Phosphate and Zinc Ricinoleate were non-irritating, Zinc Nitrate was irritating, Zinc Lactate was very irritating, and Zinc Sulfate was severely irritating. Zinc Chloride in a water solution or as a solid is an astringent and may cause potential eye irritation.

In humans, inhalation exposure via aerosol (exposure duration not specified) to 40 mg/m^3 Zinc Chloride (19.2 mg/m^3 zinc) produced a metallic taste; the particle size and other details were not provided. Another study reported that in human subjects exposed via inhalation to 4800 mg/m^3 Zinc Chloride for 30 minutes, pulmonary effects were induced (no further details).

There are case reports in the literature of poisonings following oral ingestion of large amounts of Zinc Chloride in adults and children. In one case report, a patient had multiple pruritic eruptions over his whole body; the patient had his teeth filled 3 mos prior to the onset of the rash. Patch testing with 2% Zinc Chloride was positive. The study researchers speculated that the Zinc Chloride in the dental materials was absorbed through oral mucosa or skin, and the patient was diagnosed with systemic allergic dermatitis caused by zinc.

INFORMATION SOUGHT

Any available information pertinent to the safety of the zinc salts as used in cosmetics is welcome. Particularly, dermal studies are sought.

TABLES

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

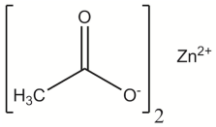
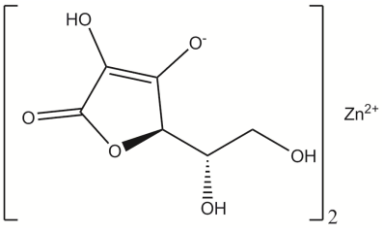
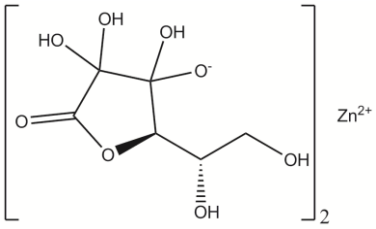
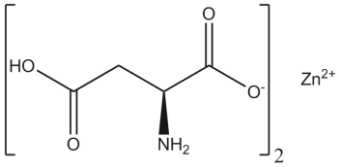
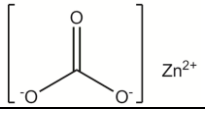
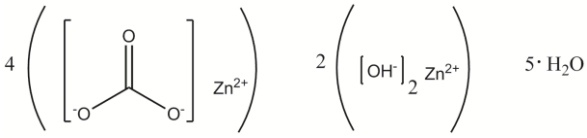
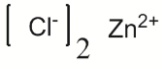
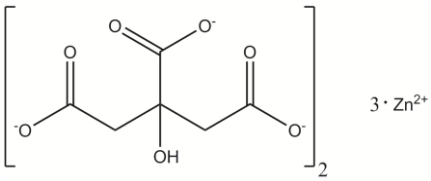
Ingredient CAS No.	Definition & Structure	Function
Zinc Acetate 557-34-6 (anhydrous) 5970-45-6 (hydrate)	Zinc Acetate is the zinc salt of acetic acid that conforms to the formula: 	cosmetic astringents; cosmetic biocides; skin protectants
Zinc Ascorbate 134343-96-7	Zinc Ascorbate is the zinc salt of Ascorbic Acid. 	antioxidants; oral care agents; skin protectants
Zinc Ascorbate Hydroxide	Zinc Ascorbate Hydroxide is the product obtained by the reaction of Ascorbic Acid and zinc chloride neutralized with sodium hydroxide. 	hair conditioning agents; light stabilizers; skin protectants; skin-conditioning agents-miscellaneous
Zinc Aspartate 36393-20-1	Zinc Aspartate is the zinc salt of Aspartic Acid. 	cosmetic biocides; hair conditioning agents; skin-conditioning agents-miscellaneous
Zinc Carbonate 3486-35-9	Zinc Carbonate is the inorganic salt that conforms to the formula: 	opacifying agents; skin protectants
Zinc Carbonate Hydroxide	Zinc Carbonate Hydroxide is an inorganic basic carbonate that conforms generally to the formula:  *According to this formula, this ingredient is the pentahydrate.*	bulking agents; pH adjusters
Zinc Chloride 7646-85-7	Zinc Chloride is the inorganic salt that conforms to the formula: 	cosmetic astringents; cosmetic biocides; drug astringents-oral health care drugs; oral care agents; oral health care drugs
Zinc Chloride Hydroxide 12167-79-2	Zinc Chloride Hydroxide is the inorganic compound that conforms to the formula:  *According to this formula, this ingredient is the monohydrate.*	bulking agents
Zinc Citrate 546-46-3	Zinc Citrate is the zinc salt of citric acid that conforms to the formula: 	cosmetic biocides; oral care agents

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

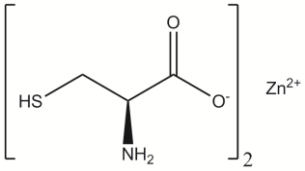
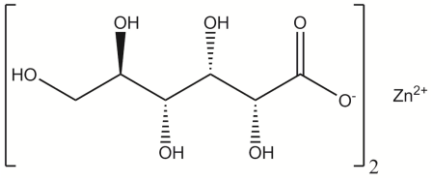
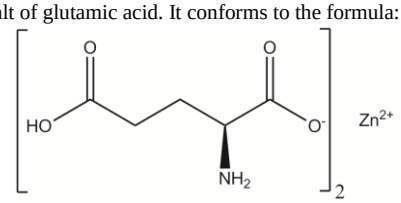
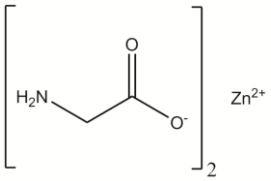
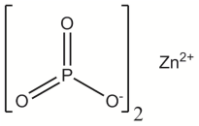
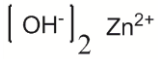
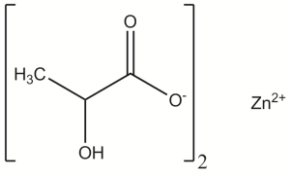
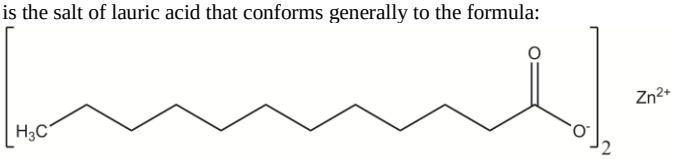
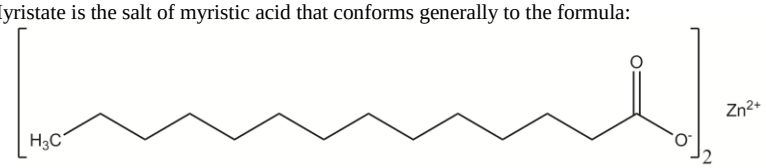
Ingredient CAS No.	Definition & Structure	Function
Zinc Cysteinate 1197186-61-0	Zinc Cysteinate is the organic salt that conforms to the formula: 	cosmetic biocides
Zinc Gluconate 4468-02-4	Zinc Gluconate is the zinc salt of gluconic acid that conforms to the formula: 	cosmetic biocides; skin-conditioning agents-miscellaneous
Zinc Glutamate 1949-15-1	Zinc Glutamate is the zinc salt of glutamic acid. It conforms to the formula: 	cosmetic biocides; hair conditioning agents; skin-conditioning agents-miscellaneous
Zinc Glycinate 14281-83-5	Zinc Glycinate is the zinc salt of glycine that conforms to the formula: 	buffering agents; pH adjusters
Zinc Hexametaphosphate 13566-15-9	Zinc Hexametaphosphate is the inorganic salt that conforms to the formula: 	buffering agents; chelating agents; corrosion inhibitors
Zinc Hydroxide 20427-58-1	Zinc Hydroxide is the inorganic compound that conforms to the formula: 	absorbents
Zinc Lactate 16039-53-5 554-05-2	Zinc Lactate is the zinc salt of lactic acid that conforms to the formula: 	cosmetic astringents; cosmetic biocides; deodorant agents
Zinc Laurate 2452-01-9	Zinc Laurate is the salt of lauric acid that conforms generally to the formula: 	anticaking agents; slip modifiers; viscosity increasing agents-non-aqueous
Zinc Myristate 16260-27-8	Zinc Myristate is the salt of myristic acid that conforms generally to the formula: 	anticaking agents; slip modifiers; viscosity increasing agents-non-aqueous

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

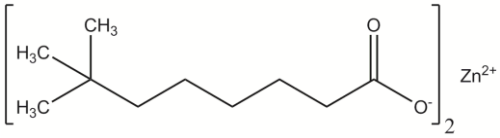
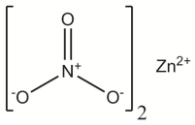
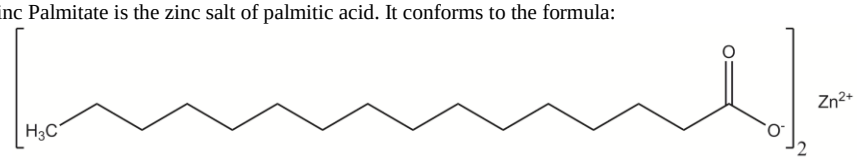
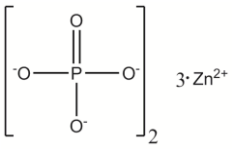
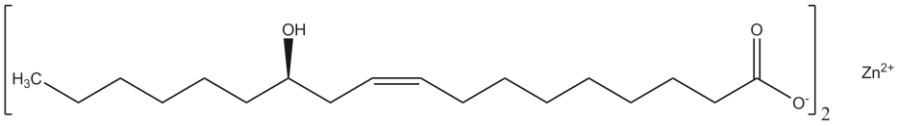
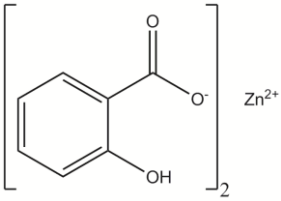
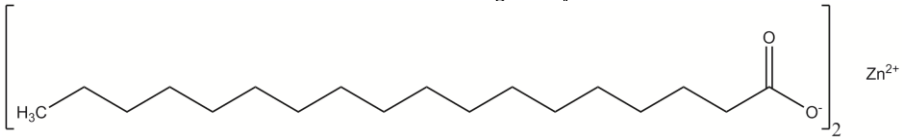
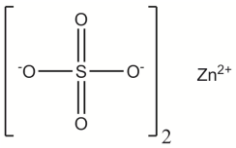
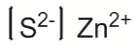
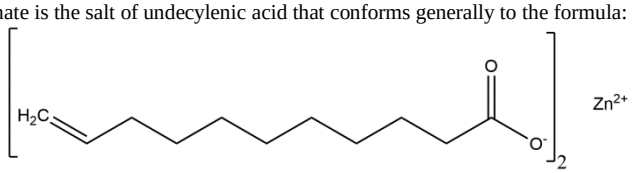
Ingredient CAS No.	Definition & Structure	Function
Zinc Neodecanoate 27253-29-8	Zinc Neodecanoate is the zinc salt of neodecanoic acid. It conforms generally to the formula: 	anticaking agents; viscosity increasing agents-non-aqueous
Zinc Nitrate 7779-88-6	Zinc Nitrate is the inorganic salt that conforms to the formula: 	skin-conditioning agents-miscellaneous
Zinc Palmitate 4991-47-3	Zinc Palmitate is the zinc salt of palmitic acid. It conforms to the formula: 	anticaking agents; slip modifiers; viscosity increasing agents-non-aqueous
Zinc Phosphate 7543-51-3	Zinc Phosphate is the inorganic compound that conforms to the formula: 	buffering agents; oral care agents
Zinc Ricinoleate 13040-19-2	Zinc Ricinoleate is the zinc salt of Ricinoleic Acid that conforms to the formula: 	anticaking agents; deodorant agents; opacifying agents
Zinc Salicylate 16283-36-6	Zinc Salicylate is the organic compound that conforms to the formula: 	preservatives
Zinc Stearate 557-05-1	Zinc Stearate is the zinc salt of stearic acid that conforms generally to the formula: 	anticaking agents; colorants; slip modifiers; viscosity increasing agents-non-aqueous
Zinc Sulfate 7446-19-7 (monohydrate) 7446-20-0 (heptahydrate) 7733-02-0 (anhydrous)	Zinc Sulfate is the inorganic salt that conforms to the formula: 	cosmetic astringents; cosmetic biocides; oral care agents
Zinc Sulfide 1314-98-3	Zinc Sulfide is the inorganic salt that conforms to the formula: 	none reported
Zinc Undecylenate 557-08-4	Zinc Undecylenate is the salt of undecylenic acid that conforms generally to the formula: 	anticaking agents; antifungal agents; cosmetic biocides

Table 2. **Constituent acids and related salts previously reviewed by the Panel**

Ingredient	Conclusion (year issued)*	Reference
CONSTITUENT ACIDS		
L-Ascorbic Acid	Safe as used (2005)	128
Aspartic Acid, Cysteine, Glutamine, Glycine	Safe as used (2013)	129
Gluconic Acid	Safe as used (2014)	130
Lactic Acid	Safe for use at concentrations ≤ 10%, at final formulation pH ≥ 3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection; safe for use in salon products at concentrations ≤ 30%, at final formulation pH ≥ 3.0, in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection (1998); reaffirmed in 2013	131
Lauric Acid, Palmitic Acid, and Stearic Acid	Safe as used (1987); reaffirmed 2006	132,133
Myristic Acid	Safe as used (1987); reaffirmed 2006 and 2010	4,132,133
Salicylic Acid	Safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection (2003)	134
SALTS		
Carbonate Salts	Safe when formulated to be non-irritating (2017)	135
Hydroxide Salts	Safe in hair straighteners and depilatories under conditions of recommended use; users should minimize skin contact. These ingredients are safe for all other present practices of use and concentrations described in the safety assessment when formulated to be non-irritating (2016)	136
Sodium Hexametaphosphate and Phosphate Salts	Safe when formulated to be non-irritating (2016)	137
Sodium Sulfate	Safe when formulated to be non-irritating (2016)	138

*Please see the original reports for further details (http://www.cir-safety.org/ingredients).

Table 3. **Physical and Chemical Properties**

Property	Value	Reference
Zinc Acetate		
Physical Form	Crystalline solid	139
Color	White	139
Formula Weight (g/mol)	183.5 (anhydrous); 219.53 (dihydrate)	43
Density (g/ml) @ 20 °C	1.74	139
Melting Point (°C)	237	140
Water Solubility (g/l)	435 (dihydrate)	43
Other Solubility (g/l)	33 in alcohol (dihydrate)	43
Log P	-1.28 (est.)	141
Zinc Ascorbate		
Formula Weight (g/mol)	415.612 (est.)	142
Log P	-1.85 (est.)	141
Zinc Ascorbate Hydroxide		
Formula Weight (g/mol)	483.64 (est.)	143
Log P	0.42 (est.)	141
Zinc Aspartate		
Formula Weight (g/mol)	329.57 (est.)	144
Log P	-3.89 (est.)	141
Zinc Carbonate		
Physical Form	Crystalline solid	145
Color	White	145
Formula Weight (g/mol)	125.42	43
Density (g/ml) @ 20 °C	4.4	146
Water Solubility (g/l) @ 15 °C	0.01	43
Other Solubility	Soluble in dilute acids, alkalies, and ammonium salt solutions	43
Log P	-2.02 (est.)	141
Zinc Carbonate Hydroxide		
Formula Weight (g/mol)	143.403 (est.)	147
Log P	-0.46 (est.)	141

Table 3. Physical and Chemical Properties

Property	Value	Reference
Zinc Chloride		
Physical Form	Granules	[43]
Color	White	[43]
Formula Weight (g/mol)	136.31	[43]
Density (g/ml) @ 25 °C	2.907	[43]
Melting Point (°C)	327.9	[43]
Boiling Point (°C)	732	[43]
Water Solubility (g/l) @ 25°C	4320	[43]
Other Solubility	Soluble in 2% $HCl_{(aq)}$, alcohol, glycerol, acetone	[43]
Log P	0.15 (est.)	[141]
Zinc Chloride Hydroxide		
Formula Weight (g/mol)	117.837 (est.)	[148]
Log P	-0.47 (est.)	[141]
Zinc Citrate		
Formula Weight (g/mol)	574.43	[43]
Water Solubility	Slightly soluble in water (dihydrate)	[43]
Other Solubility	Soluble in dilute mineral acids and in alkali hydroxides (dihydrate)	[43]
Log P	-2.09 (est.)	[141]
Zinc Cysteinate		
Formula Weight (g/mol)	185.5446	[149]
Log P	-7.50 (est.)	[141]
Zinc Gluconate		
Physical Form	Granular or crystalline powder	[49]
Color	White	[49]
Formula Weight (g/mol)	455.68	[49]
Melting Point (°C)	172-175	[150]
Water Solubility	Freely soluble	[49]
Other Solubility	Very slightly soluble in alcohol	[49]
Log P	-7.41 (est.)	[141]
Zinc Glutamate		
Formula Weight (g/mol)	210.494 (est.)	[151]
Log P	-2.04 (est.)	[141]
Zinc Glycinate		
Formula Weight (g/mol)	213.498 (est.)	[152]
Melting Point (°C)	> 300	[153]
Log P	-3.21 (est.)	[141]
Zinc Hexametaphosphate		
Formula Weight (g/mol)	223.322 (est.)	[154]
Log P	-1.72 (est.)	[141]
Zinc Hydroxide		
Formula Weight (g/mol)	101.41 (est.)	[155]
Density (g/ml)	3.053	[25]
Melting Point (°C)	125	[25]
Water Solubility	Very slightly soluble	[25]
Other Solubility	Soluble in acid and alkali	[25]
Log P	-0.77 (est.)	[141]
Zinc Lactate		
Physical Form	Crystals (trihydrate)	[43]
Formula Weight (g/mol)	243.52	[156]
Water Solubility	Soluble (trihydrate)	[43]
Log P	-2.97 (est.)	[141]
Zinc Laurate		
Formula Weight (g/mol)	464.008 (est.)	[156]
Density (g/ml)	1.09	[157]
Melting Point (°C)	130-135	[157]
Log P	8.54 (est.)	[141]
Zinc Myristate		
Formula Weight (g/mol)	520.116	[158]
Density (g/ml) @ 20 °C and 760 mmHg	1.16	[159]
Melting Point (°C)	130-134	[159]
Log P	10.51 (est.)	[141]

Table 3. **Physical and Chemical Properties**

Property	Value	Reference
Zinc Neodecanoate		
Formula Weight (g/mol)	409.916 (est.)	160
Log P	6.14 (est.)	141
Zinc Nitrate		
Physical Form	Powder	44
Color	White	44
Formula Weight (g/mol)	189.42	43
Density (g/ml)	2.065 (hexahydrate)	43
Melting Point (°C)	~36 (hexahydrate)	43
Water Solubility	Soluble in water (hexahydrate)	43
Other Solubility	Freely soluble in alcohol (hexahydrate)	43
Log P	-0.51 (est.)	141
Zinc Palmitate		
Formula Weight (g/mol)	576.224	161
Density (g/ml)	1.14	162
Melting Point (°C)	129-135	162
Log P	12.47 (est.)	141
Zinc Phosphate		
Physical Form	Powder	43
Color	White	43
Formula Weight (g/mol)	386.17	43
Density (g/ml)	3.16 (experimental)	163
Water Solubility	Insoluble	43
Other Solubility	Insoluble in alcohol; soluble in dilute mineral acids, acetic acid, ammonia, and alkali hydroxide solutions	43
Log P	-0.77 (est.)	141
Zinc Ricinoleate		
Formula Weight (g/mol)	660.298 (est.)	164
Log P	11.34 (est.)	141
Zinc Salicylate		
Physical Form	Crystal powder or needles	43
Formula Weight (g/mol)	339.64	43
Water Solubility	Soluble	43
Other Solubility	Soluble in alcohol	43
Log P	3.18 (est.)	141
Zinc Stearate		
Physical Form	Powder	49
Color	White	49
Formula Weight (g/mol)	632.3	49
Density (g/ml)	1.1	165
Melting Point (°C)	120	43
Water Solubility	Practically insoluble	49
Other Solubility	Insoluble in alcohol and ether; soluble in benzene	43
Log P	14.44 (est.)	141
Zinc Sulfate		
Physical Form	Transparent prisms, small needles, or granular crystalline powder	49
Color	Colorless	49
Formula Weight (g/mol)	179.45 (monohydrate); 287.54 (heptahydrate)	49
Density (g/ml)	1.97 (heptahydrate)	43
Melting Point (°C)	100 (heptahydrate)	43
Water Solubility	Soluble (mono- and heptahydrate)	49
Other Solubility	Insoluble in alcohol (mono- and heptahydrate); soluble in glycerine (heptahydrate)	49
Log P	-0.07 (est.)	141
Zinc Sulfide		
Physical Form	Powder	43
Color	White, gray or yellow	43
Formula Weight (g/mol)	97.47	43
Density (g/ml)	4.0	166
Melting Point (°C)	1700	166
Water Solubility	Insoluble in water and alkalies	43
Other Solubility	Soluble in dilute mineral acids	43
Log P	1.53 (est.)	141

Table 3. Physical and Chemical Properties

Property	Value	Reference
Zinc Undecylenate		
Formula Weight (g/mol)	431.922 (est.)	[167]
Melting Point (°C)	115-116	[168]
Log P	7.29 (est.)	[141]

Table 4. Methods of Manufacture

Ingredient	Method
Zinc Acetate	prepared by reacting zinc oxide with acetic acid [39]
Zinc Carbonate	prepared grinding the mineral smithsonite [40]
Zinc Chloride	can be made by reacting aqueous hydrochloric acid and zinc scrap materials or roasted ore [41] may be achieved by combining zinc and hydrogen chloride gas at 700 °C reaction of zinc oxide with hydrochloric acid
Zinc Chloride Hydroxide	prepared by a 24-hour hydrolysis reaction of Zinc Chloride with sodium hydroxide at 60 °C [42] reaction of ammoniated Zinc Chloride and water are reacted with Zinc Chloride in a crystallization process, yielding Zinc Chloride Hydroxide monohydrate (91% to 95%) and zinc diammine chloride (5% to 9%); zinc diammine chloride is partially removed by water in subsequent steps while the remaining portion undergoes conversion to zinc oxide (< 9%) [38]
Zinc Citrate	formed from Zinc Carbonate and citric acid [43]
Zinc Lactate	prepared from lactic acid and Zinc Carbonate [43]
Zinc Nitrate	can be prepared by reacting nitric acid with zinc or zinc oxide [44]
Zinc Salicylate	prepared from Zinc Sulfate and sodium salicylate [43]
Zinc Stearate	prepared from Zinc Chloride and stearic acid [43] can also be prepared by reacting sodium stearate with a Zinc Sulfate solution [45]
Zinc Sulfate	can be prepared by combining dilute sulfuric acid with zinc hydroxide, followed by crystallization of the supernatant with acetone [48] reaction of sulfuric acid and zinc oxide [46]
Zinc Sulfide	reacting sodium sulfide and Zinc Sulfate, followed by passing hydrogen sulfide through a zinc salt aqueous solution [47]
Zinc Undecylenate	combination of zinc oxide and undecylic acid (in an ethanol solution); an ethanol wash is used after filtering the residue and then the product is dried at 115°C [48]

Table 5. Current frequency and concentration of use of zinc salts[2-5,7,55,56]

	# of Uses	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*
	Zinc Acetate**		**Zinc Acetate**		**Zinc Ascorbate**	
	2009	**2010**	**2017**	**2016**	**2017**	**2016**
Totals*	**1**	**0.4**	**2**	**NR**	**NR**	**0.01-5**
Duration of Use						
Leave-On	*NR*	*NR*	*NR*	*NR*	*NR*	*0.047-0.3*
Rinse-Off	*1*	*0.4*	*2*	*NR*	*NR*	*0.01-5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	0.047
Incidental Ingestion	1	0.4	2	NR	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 1[a]	spray: NR possible: 0.4[a]	spray: NR possible: 2[a]	NR	NR	spray: 0.05 possible: NR
Incidental Inhalation-Powder	NR	NR	powder: NR possible: NR	NR	NR	powder: 0.095 possible: 0.05-0.1[c]
Dermal Contact	NR	NR	NR	NR	NR	0.047-0.3
Deodorant (underarm)	NR	NR	NR	NR	NR	not spray: 0.3
Hair - Non-Coloring	NR	NR	NR	NR	NR	0.01-5
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	0.4	2	NR	NR	0.05
Baby Products	NR	NR	NR	NR	NR	0.01

Table 5. **Current frequency and concentration of use of zinc salts**[2-5,7,55,56]

	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)
	Zinc Aspartate		**Zinc Carbonate**		**Zinc Chloride**	
	2017	**2016**	**2017**	**2016**	**2017**	**2016**
Totals*	**25**	**NR**	**2**	**1.6**	**76**	**0.000095-0.47**
Duration of Use						
Leave-On	*8*	*NR*	*2*	*NR*	*62*	*0.0001-0.47*
Rinse-Off	*17*	*NR*	*NR*	*1.6*	*14*	*0.000095-0.21*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	1	NR	1	NR	8	0.039-0.064
Incidental Ingestion	NR	NR	NR	NR	9	0.088
Incidental Inhalation-Spray	spray: NR possible: 5[a], 2[b]	NR	spray: NR possible: 1[b]	NR	spray: 1 possible: 15[a], 3[b]	spray: NR possible: 0.003-0.088[a]
Incidental Inhalation-Powder	powder: NR possible: 2[b]	NR	powder: NR possible: 1[b]	NR	powder: NR possible: 3[b]	powder: 0.04-0.47 possible: NR
Dermal Contact	9	NR	2	NR	64	0.00075-0.47
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	16	NR	NR	1.6	3	0.000095-0.21
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	9	0.088
Baby Products	NR	NR	NR	NR	NR	NR

	Zinc Citrate**		**Zinc Citrate**		**Zinc Gluconate**	
	2011	**2011**	**2017**	**2016**		
Totals*	**9**	**0.05-2**	**13**	**0.05-2**	**318**	**0.000005-3**
Duration of Use						
Leave-On	*5*	*0.05*	*5*	*NR*	*243*	*0.00024-3*
Rinse-Off	*4*	*0.3-2*	*8*	*0.05-2*	*73*	*0.00005-0.5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*2*	*0.000005*
Exposure Type						
Eye Area	NR	NR	NR	NR	35	0.0048-3
Incidental Ingestion	4	0.3-2	8	0.28-2	10	0.1
Incidental Inhalation-Spray	NR	NR	NR	spray: NR possible: 0.28[a]	spray: NR possible: 76[a], 65[b]	spray: NR possible: 0.001[a]
Incidental Inhalation-Powder	NR	powder: 0.05	NR	NR	powder: NR possible: 65[b]	powder: NR possible: 0.001-1[c]
Dermal Contact	5	0.05	5	0.05	282	0.000005-3
Deodorant (underarm)	4[a]	NR	3[a]	NR	14[a]	NR
Hair - Non-Coloring	NR	NR	NR	NR	22	0.00005-0.5
Hair-Coloring	NR	NR	NR	NR	4	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	4	0.3-2	8	0.05-2	19	0.000005-0.1
Baby Products	NR	NR	NR	NR	NR	NR

	Zinc Glycinate		**Zinc Hydroxide**		**Zinc Lactate**	
	2017	**2016**	**2017**	**2016**	**2017**	**2016**
Totals*	**NR**	**0.009**	**2**	**NR**	**1**	**0.25-1.8**
Duration of Use						
Leave-On	*NR*	*0.009*	*2*	*NR*	*NR*	*NR*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*1*	*0.25-1.8*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	1	0.25-0.44
Incidental Inhalation-Spray	NR	NR	spray: NR possible: 1[a], 1[b]	NR	spray: NR possible: 1[a]	spray: NR possible: 0.25[a]
Incidental Inhalation-Powder	NR	NR	powder: NR possible: 1[b]	NR	NR	NR
Dermal Contact	NR	0.009	2	NR	NR	1.8
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	1	0.25-0.44
Baby Products	NR	NR	NR	NR	NR	NR

Table 5. **Current frequency and concentration of use of zinc salts**[2-5,7,55,56]

	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)
	Zinc Laurate		**Zinc Myristate****		**Zinc Myristate**	
	2017	**2016**	**2007**	**2006**	**2017**	**2016**
Totals*	**115**	**1-7**	**122**	**0.00005-39526**	**59**	**0.005-20**
Duration of Use						
Leave-On	*97*	*1-7*	*122*	*0.00005-39526*	*59*	*0.005-20*
Rinse-Off	*17*	*1.2*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*1*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	56	NR	60	0.05-6	25	0.51-20
Incidental Ingestion	NR	NR	NR	5	NR	0.063-5
Incidental Inhalation-Spray	spray: NR possible: 2[b]	NR	NR	spray: NR possible: 0.1[a], 5[b]	NR	NR
Incidental Inhalation-Powder	powder: 8 possible: 2[b]	powder: 3-7	powder: 18	powder: 39526 possible: 5[b]	powder: 18 possible: NR	powder: 2-20 possible: 5-15[c]
Dermal Contact	105	1-7	117	0.001-39526	59	0.51-20
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	10	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	5	0.00005	NR	0.005-0.035
Mucous Membrane	5	NR	NR	5	NR	0.063-5
Baby Products	NR	NR	NR	NR	NR	NR

	Zinc Phosphate		**Zinc Ricinoleate****		**Zinc Ricinoleate**	
	2017	**2016**	**2002**	**2004**	**2017**	**2016**
Totals*	**NR**	**1**	**3**	**1-2**	**27**	**0.15-2.3**
Duration of Use						
Leave-On	*NR*	*NR*	*2*	*1-2*	*25*	*0.15-2.3*
Rinse-Off	*NR*	*1*	*1*	*NR*	*2*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	1	NR	NR	2	1.1
Incidental Inhalation-Spray	NR	NR	NR	spray: 1 possible: 1[b]	spray: NR possible: 1[a]	NR
Incidental Inhalation-Powder	NR	NR	NR	powder: NR possible: 1[b]	NR	powder: NR possible: 0.15[c]
Dermal Contact	NR	NR	3	1-2	23	0.15-2.3
Deodorant (underarm)	NR	NR	2[a]	2[a]	21[a]	spray: 0.82-2.3 not spray: 0.82-2
Hair - Non-Coloring	NR	NR	NR	1	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	1	NR
Mucous Membrane	NR	1	NR	NR	3	1.1
Baby Products	NR	NR	NR	NR	NR	NR

	Zinc Salicylate		**Zinc Stearate****		**Zinc Stearate**	
	2017	**2016**	**2001**	**2001**	**2017**	**2016**
Totals*	**NR**	**0.47**	**746**	**0.5-51**	**2321**	**0.2-32**
Duration of Use						
Leave-On	*NR*	*0.47*	*742*	*0.5-51*	*2312*	*0.2-32*
Rinse-Off	*NR*	*NR*	*2*	*1*	*7*	*0.28-3.3*
Diluted for (Bath) Use	*NR*	*NR*	*2*	*3*	*2*	*NR*
Exposure Type						
Eye Area	NR	NR	346	1-16	1397	1-32
Incidental Ingestion	NR	NR	2	3	5	0.5-2
Incidental Inhalation-Spray	NR	NR	spray: NR possible: 2[a], 5[b]	spray: 2 possible: 1-2[a], 1-2[b]	spray: NR possible: 10[a], 8[b]	spray: 0.3 possible: NR
Incidental Inhalation-Powder	NR	NR	powder: 236 possible: 5[b], 2[c]	powder: 2-24 possible: 1-2[b], 0.5[c]	powder: 456 possible: 8[b], 1[c]	powder: 1.1-14 possible: 0.2-1[c]
Dermal Contact	NR	0.47	738	0.5-51	2308	0.2-32
Deodorant (underarm)	NR	not spray: 0.47	NR	2[a]	NR	NR
Hair - Non-Coloring	NR	NR	1	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	6	3.3
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	4	3	7	0.5-2
Baby Products	NR	NR	2	0.5	1	NR

Table 5. **Current frequency and concentration of use of zinc salts**[2-5,7,55,56]❁

	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)
	Zinc Sulfate* **		**Zinc Sulfide**		**Zinc Undecylenate**	
	2017	**2016**	**2017**	**2016**	**2017**	**2016**
Totals*	**134**	**0.0001-1**	**10**	**6.6**	**NR**	**0.25**
Duration of Use						
Leave-On	*75*	*0.0001-1*	*10*	*6.6*	*NR*	*0.25*
Rinse-Off	*59*	*0.0003-0.15*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	11	0.02	NR	NR	NR	NR
Incidental Ingestion	1	NR	3	NR	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 14[a], 20[b]	spray: NR possible: 0.003[a]	NR	NR	NR	spray: NR possible: 0.25[b]
Incidental Inhalation-Powder	powder: 5 possible: 20[b]	powder: 0.02 possible: 0.0008-0.12[c]	NR	NR	NR	powder: NR possible: 0.25[b]
Dermal Contact	101	0.0003-1	3	NR	NR	0.25
Deodorant (underarm)	NR	0.0015	NR	NR	NR	NR
Hair - Non-Coloring	32	0.003-0.15	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	0.0001-0.001	4	6.6	NR	NR
Mucous Membrane	13	0.0003-0.057	3	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

❁ Concentration of use data from the Council Industry survey is pending for Zinc Ascorbate Hydroxide; the data will be added to the report when they become available.

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

** Ingredient was reviewed previously; current use and use from previous report are included for comparison.

*** Frequency of use data from the VCRP was reported separately for Zinc Sulfate and zinc sulfate anhydrous, but the above frequency of use totals for Zinc Sulfate are the sum of uses for both forms of the ingredient.

[a] Includes products that can be sprays, but it is not known whether the reported uses are sprays.

[b] Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation.

[c] Includes products that can be powders, but it is not known whether the reported uses are powders.

NR – no reported use.

Table 6. **Ingredients Not Reported to Be in Use**

Zinc Carbonate Hydroxide	Zinc Hexametaphosphate
Zinc Chloride Hydroxide	Zinc Neodecanoate
Zinc Cysteinate	Zinc Nitrate
Zinc Glutamate	Zinc Palmitate

Table 7. Appearance of Ingredients in Code of Federal Regulations

Ingredient	Non-Cosmetic Use	References*
Zinc Salts	-Food additives permitted for direct addition to food for human consumption; zinc salts < 500 ppm as zinc	21CFR172.325
	-Indirect food additives; adjuvants, production aids, sanitizers; rosins and rosin derivatives; zinc salts may be used in saponification of rosins	21CFR178.3870
Zinc Salts of Fatty Acids	-Ingredient food additives, polymers, rubber articles; zinc salts of fatty acids may be used as activators (≤ 5% by weight of rubber product)	21CFR177.2600
Zinc Acetate	-Indirect food additive, adhesives and components of coatings (no limitations for Zinc Acetate specified)	21CFR175.105
	-Requirements for specific new drugs or devices; drug products containing certain active ingredients offered OTC; there are inadequate data to establish safety and effectiveness of Zinc Acetate in skin protectant drug products (only for wound healing claims) and in diaper rash drug products	21CFR310.545
	-Skin protectant drug products for OTC human use; Zinc Acetate (0.1% to 2%) may be used as an active ingredient in skin protectant drug products	21CFR347.10
	-Labeling of skin protectant drug products for OTC human use; the labeling for products containing Zinc Acetate states "[bullet] children under 2 years: ask a doctor"	21CFR347.50
	-Zinc Acetate is GRAS as a trace mineral added to animal feeds using good feeding practice	21CFR582.80
Zinc Carbonate	-Indirect food additive, paper and paperboard components; Zinc Carbonate may be used as a colorant only	21CFR176.170
	-Ingredient food additives, polymers, rubber articles; Zinc Carbonate may be used as a filler	21CFR177.2600
	-Indirect food additives; adjuvants, production aids, and sanitizers; Zinc Carbonate may be used as a colorant for polymers	21CFR178.3297
	-Requirements for specific new drugs or devices; drug products containing certain active ingredients offered OTC; there are inadequate data to establish safety and effectiveness of Zinc Carbonate in diaper rash drug products	21CFR310.545
	-Skin protectant drug products for OTC human use; Zinc Carbonate (0.2% to 2%) may be used as an active ingredient in skin protectant drug products	21CFR347.10
	-Zinc Carbonate is GRAS as a trace mineral added to animal feeds using good feeding practice	21CFR582.80
Zinc Chloride	-Zinc Chloride is GRAS as a substance migrating to food from cotton and cotton fabrics in dry food packaging	21CFR182.70
	-Zinc Chloride is GRAS as a nutrient used for human consumption when used with GMP	21CFR182.8985
	-Requirements for specific new drugs or devices; drug products containing certain active ingredients offered OTC; there are inadequate data to establish safety and effectiveness of Zinc Chloride in astringent drug products	21CFR310.545
	-Zinc Chloride is GRAS as a trace mineral added to animal feeds using good feeding practice	21CFR582.80; 21CFR582.5985
Zinc Gluconate	-Zinc Gluconate is GRAS as a nutrient used for human consumption when used with GMP	21CFR182.8988
	-Implantation or injectable dosage from new animal drugs; indication for use is intratesticular injection for chemical sterilization of 3- to 10-month-old male dogs; 13.1 mg zinc supplied as Zinc Gluconate is present in each milliliter of solution	21CFR522.2690
	-Zinc Gluconate is GRAS as a nutrient or dietary supplement for animals when using GMP or feeding practice	21CFR582.5988
Zinc Hydroxide	-Indirect food additive, paper and paperboard components, defoaming agents used in the manufacture of paper and paperboard; Zinc Hydroxide used in the formation of soaps	21CFR176.210

Table 7. Appearance of Ingredients in Code of Federal Regulations

Ingredient	Non-Cosmetic Use	References*
Zinc Nitrate	-Indirect food additive, adhesives and components of coatings (no limitations for Zinc Nitrate specified)	21CFR175.105
Zinc Palmitate	-Indirect food additive; Zinc Palmitate may be used as an antioxidant and/or stabilizer in polymers	21CFR178.2010
Zinc Salicylate	-Indirect food additive; Zinc Salicylate may be used as an antioxidant and/or stabilizer in polymers with the stipulation to be used in only rigid polyvinyl chloride polymers or copolymers and total salicylates (calculated as acid) ≤ 0.3% by weight in these polymers	21CFR178.2010
Zinc Stearate	-Indirect food additive, paper and paperboard components	21CFR176.180
	-Indirect food additive, polymers, food contact surfaces, melamine-formaldehyde resins (1:3 molar ratio of melamine to formaldehyde in aqueous solution); urea-formaldehyde resins (1:2 molar ratio of urea to formaldehyde in aqueous solution); phenolic resins; Zinc Stearate may be used as a lubricant in these resins	21CFR177.1460; 21CFR177.1900; 21CFR177.2410
	-Indirect food additive; Zinc Stearate may be used as antioxidant and/or stabilizer in polymers	21CFR178.2010
	-Zinc Stearate is GRAS as a nutrient used for human consumption when used with GMP	21CFR182.8994
	-Requirements for specific new drugs or devices; drug products containing certain active ingredients offered OTC; there are inadequate data to establish safety and effectiveness of Zinc Stearate in topical acne drug products	21CFR310.545
	-Interpretative statements re warnings on drugs and devices for OTC sale, warning and caution statements for drugs; Zinc Stearate dusting powders has the following recommended warning and caution statement: "Keep out of reach of children; avoid inhaling. If swallowed, get medical help or contact a Poison Control Center right away."	21CFR369.20
	-Zinc Stearate (prepared from stearic acid not containing chick-edema factor) is GRAS as a nutrient or dietary supplement for animals when using GMP or feeding practice	21CFR582.5994
	-Occupational safety and health standards, toxic and hazardous substances, air contaminants; Zinc Stearate shall not exceed the 8-hour Time Weighted Average in any 8-hour work shift of a 40-hour work week; Zinc Stearate air contaminant limits are total dust (15 mg/m^3) and respirable fraction (5 mg/m^3)	29CFR1910.1000; 29CFR1915.1000
Zinc Sulfate	-Zinc Sulfate is GRAS as a substance migrating to food from paper and paperboard products in food packaging	21CFR182.90
	-Zinc Sulfate is GRAS as a nutrient used for human consumption when used with GMP	21CFR182.8997
	-Requirements for specific new drugs or devices; drug products containing certain active ingredients offered OTC; there are inadequate data to establish safety and effectiveness of Zinc Sulfate in the following types of drug products: external analgesic and anesthetics, specifically for treatment of fever blister and cold sores; poison treatment; astringents	21CFR310.545
	-Ophthalmic drug products for OTC human use; Zinc Sulfate (0.25%) may be used as an active ingredient in ophthalmic astringents	21CFR347.50
	-New animal drugs for use in animal feeds; Zinc Sulfate (variable concentration, 0.76% or 1.47%) may be used in free-choice animal feed containing fenbendazole given to cattle	21CFR558.258
	-Zinc Sulfate (hydrated or anhydrous forms) is GRAS as a trace mineral added to animal feeds using good feeding practice	21CFR582.80; 21CFR582.5997
Zinc Sulfide (luminescent color additive, contains a copper activator)	-Produces yellow-green phosphorescence (530 nm) after excitation by light; CFR citation specifies Zinc Sulfide with purity ≥ 99.8% in this application; safe to use for facial makeup preparations and nail polish with concentrations ≤ 10% by weight in final product; use should be for infrequent occasions (e.g., Halloween) and not daily use; label requires expiration date and the following statement, "Do not use in the area of the eye."	21CFR73.2995

Table 7. Appearance of Ingredients in Code of Federal Regulations

Ingredient	Non-Cosmetic Use	References*
Zinc Sulfide	-Indirect food additive, adhesives and components of coatings (no limitations for Zinc Sulfide specified)	21CFR175.105
	--Ingredient food additives, polymers, rubber articles; Zinc Sulfide may be used as a filler	21CFR177.2600
	-Indirect food additives; adjuvants, production aids, and sanitizers; Zinc Sulfide (≤ 10% by weight) may be used as a colorant for polymers	21CFR178.3297
	-Indirect food additive; adjuvants, production aids, and sanitizers; lubricants with incidental food contact; Zinc Sulfide (≤ 10% by weight of lubricant) may be used in lubricants utilized in machinery for producing, packing, etc. food	21CFR178.3570
	-Requirements for specific new drugs or devices; drug products containing certain active ingredients offered OTC; there are inadequate data to establish safety and effectiveness of Zinc Sulfide in topical acne drug products	21CFR310.545
Zinc Undecylenate	-Topical antimicrobial drug products for OTC human use; Zinc Undecylenate (total undecylenate concentration of 10% to 25%) may be used as an active ingredient in topical antifungal drug products	21CFR333.210

GMP = good manufacturing practice; GRAS = generally recognized as safe; OTC = over-the-counter

Table 8. **Dermal Penetration Studies**

Test Substance(s)	Species	Sample Type or Test Population-Sex			Results	Reference
DERMAL PENETRATION						
IN VITRO						
Animal						
Zinc Sulfate (monohydrate)	Pig	Stratum corneum, stratum germinativum, and blood vessel containing dermis collected using a dermatome; n=6 skin samples evaluated (no further details provided)	40 mg/ml in water, 1 mg/cm^2 concentration applied to skin samples	Skin samples prepared at 1 mm thickness and mounted into Teflon flow-through diffusion cells; diffusion cells rinsed continuously with receptor fluid (0.9% sodium chloride in aqua bidest containing antibiotics); test substance applied for 8 h (no occlusion) and washed with shampoo; receptor fluid analyzed for zinc content at 0, 2, 4, 6, 8, 16, 24, 40, 48, 64, and 72 h using atomic absorption spectroscopy (10 ng/ml detection limit); skin samples and rinsing fluid also evaluated for zinc content	Study authors reported 0.3% zinc in receptor fluid, 1.3% zinc in horny layer, 0% zinc in residual skin for a total of 1.6% potentially absorbed zinc from applied concentration; percentages reflect correction for background zinc levels in skin and receptor fluid (levels not provided); total zinc recovery in experiment between 82.0% to 109.6% of applied amount	[20]
IN VIVO						
Animal						
Zinc Chloride	Rat/ Sprague-Dawley	n=5-7/group	Groups 1 & 2: oily substance containing < 4 ppm zinc; Groups 3 & 4: oily substance containing 7500 ppm zinc supplied as Zinc Chloride	After pregnancies confirmed, females fed diet deficient in zinc (fed diet with adequate zinc prior to and during mating), food and water available ad libitum; at beginning of zinc deficient diet 0.4 ml test substance applied to shaved skin and covered with gauze and bandages; test substance applied to animals in groups 1 & 3 at 8 am and in groups 2 & 4 at 12 midnight; animals in groups 1-4 killed 24 h after starting zinc deficient diet; animals receiving diet containing sufficient amounts of zinc killed at time zero (beginning of study) to serve as controls for plasma zinc levels	Study researchers confirmed no oily test substance leaked through bandage creating potential oral exposure route for animals; results indicated zinc percutaneously absorbed through skin; plasma zinc levels reported as follows: Control diet at time zero: 114.6 µg/ 100 ml, statistically significantly higher than Groups 1 & 2; Group 1 (zinc-deficient diet with 24 h topical treatment without zinc): 63.2 µg/ 100 ml; Group 2 (zinc-deficient diet with 8 h topical treatment without zinc): 74.6 µg/ 100 ml ; Group 3 (zinc-deficient diet with 24 h topical zinc treatment): 182.5 µg/ 100 ml, statistically significantly higher than Groups 1, 2, 4, and control group; Group 4 (zinc-deficient diet with 8 h topical zinc treatment): 114.8 µg/ 100 ml, statistically significantly higher than Groups 1 & 2	[71]
Zinc Chloride (^{65}Zn radiolabeled)	Guinea Pig	Males and females, n=?	0.005M (pH 5.8), 0.08M (pH 6.1, 5.7, 1.8), 0.239M (pH 5.7), 0.398M (pH 5.6), 0.753M (pH 5.3), 4.87M (pH 3.7); water vehicle	Test substance applied to back skin (no indication whether skin shaved); radioactivity in skin determined by scintillation detector	Percent absorption during 5 h reported as follows: 0.005M < 1%; 0.08M pH 6.1 < 1% up to 2.9%; 0.08M pH 5.7 < 1% up to 1.9%; 0.08M pH 1.8 < 1% up to 3.9%; 0.239M pH 5.7 < 1 % up to 3.9%; 0.398M pH 5.6 < 1% up to 3.9%; 0.753M pH 5.3 < 1% up to 2.9%; 4.87M pH 3.7 < 1% up to 3.9%	[72]

Table 8. **Dermal Penetration Studies**

Test Substance(s)	Species	Sample Type or Test Population-Sex			Results	Reference
Zinc Sulfate, Zinc Undecylenate (each labeled with 131 µCi/mole ^{65}Zn)	Rabbit	n=2	2.5 mg Zinc Sulfate or 2.5 mg Zinc Undecylenate (vehicle=glycerin: propylene glycol, 1:1)	Test substance applied to 1 inch diameter circular regions of shaved back skin of 2 animals; skin sites on left side of back treated with 1 application and sites on right side treated with 2 applications made 24 h apart; treated sites excised and assayed for ^{65}Zn	By 6 h after single application of radiolabeled Zinc Sulfate 65% of applied radioactivity detected and by 24 h 19% of applied radioactivity detected; by 6 h after single application of radiolabeled Zinc Undecylenate 37% of applied radioactivity detected and by 24 h 23% detected; by 6 h after double application of radiolabeled Zinc Sulfate 3% of applied radioactivity detected and by 24 h 12% detected; by 6 h after double application of radiolabeled Zinc Undecylenate 6% of applied radioactivity detected and by 24 h 8% detected; radioautographic analysis detected ^{65}Zn in high concentrations 6 h after double applications of radiolabeled Zinc Undecylenate in cuticular and cortical regions of hair shaft and subdermal muscle; detection of ^{65}Zn low in dermis and epidermis; radioautographic analysis detected ^{65}Zn near areas stained to locate sulfhydryl and disulfide groups in hair shaft cortex and hair papilla; sulfhydryl and disulfide reactions with ^{65}Zn also noted in epidermis; study researchers suggested ^{65}Zn diffusion through hair follicles facilitated uptake of ^{65}Zn in skin	[48]

PBS = Phosphate Buffered Saline; TEWL = Transepidermal Water Loss

Table 9. **Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)**

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
ANIMAL						
Dermal						
Zinc Chloride (^{65}Zn radiolabeled, 0.5-1.1 mCi/ml)	Rat/ Sprague-Dawley	n=?	Stock solution of test substance (concentration not specified)	25 µl of test substance applied to shaved 3 cm^2 skin area on both sides of back and occlusively covered; blood samples collected from tails at various intervals post-application; animals killed 10 min and 4 and 24 h post-application	^{65}Zn activity in blood achieved a maximum 1 h post-application; ^{65}Zn activity detected in coagulum, serum, liver, and heart as soon as 10 min post-application and peaked 4 h post-application, decreasing by 24 h	[73]
Zinc Chloride (^{65}Zn radiolabeled, 0.5-1.1 mCi/ml)	Rat/ Sprague-Dawley	n=6-7 animals/group	1.3 µg zinc/ml supplied as Zinc Chloride at pH 1 or pH 4	25 µl of test substance applied to shaved 3 cm^2 skin area on both sides of back and occlusively covered; blood samples collected from tails at various intervals post-application; animals killed 2 h post-application; autoradiography performed on skin samples	^{65}Zn activity in serum achieved a maximum 0.5 h (pH 4) and 1 h (pH 1) post-application; ^{65}Zn relative activity highest in liver (pH 1 and pH 4) and less activity detected in serum, coagulum, heart, and testis (pH 1 and pH 4); percent of absorbed activity detected in skin with pH 1, pH 4 (4.1%, 1.6%), carcass (50.2%, 53.5%), liver (28.8%, 24.7%), and gastrointestinal tract (21.0%, 21.8%), respectively; ^{65}Zn activity from autoradiograph detected in dermis (near hair follicles), panniculus carnosus, and epidermis	[73]

Table 9. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Zinc Chloride (^{65}Zn radiolabeled, 0.5-1.1 mCi/ml)	Rat/ Sprague-Dawley	n=6-7 animals/group	1.1 or 125 µg zinc/ml supplied as Zinc Chloride at pH 1	25 µl of test substance applied to shaved 3 cm^2 skin area on both sides of back and occlusively covered; blood samples collected from tails at various intervals post-application; animals killed 2 h post-application; autoradiography performed on skin samples	Small and slightly higher ^{65}Zn activity observed with 1.1 µg/ml than 125 µg/ml concentration in serum and coagulum at 0.5 h and 2 h; percent of absorbed ^{65}Zn activity in skin 6.1% (1.1 µg/ml) and 3.6% (125 µg/ml); ^{65}Zn activity from autoradiograph detected in dermis (near hair follicles), panniculus carnosus, and epidermis	[73]
				Oral		
Zinc Acetate (dihydrate)	Dog/ Beagle	n=6	0, 2, 4 mg/kg/day	3 consecutive phases of study conducted; each phase consisted of adaptation to diet for first week and urine and feces collection throughout second week; during phase 1 no additional supplementation of test substance to regular diet; in phase 2, 2 mg/kg/day test substance supplementation added to regular diet; in phase 3, 4 mg/kg/day test substance supplementation added to regular diet; regular diet contained 180 mg/kg zinc; blood samples collected prior to and after each phase	Mean fecal zinc levels: 693 µg/kg (control), 1325 µg/kg (2 mg/kg/day), 1641 µg/kg (4 mg/kg/day); mean urine zinc levels: 686 µg/kg (control), 1319 µg/kg (2 mg/kg/day), 1729 µg/kg (4 mg/kg/day); mean apparent absorption levels: 0.35 (control), 0.21 (2 mg/kg/day), 0.30 (4 mg/kg/day); mean zinc concentrations in blood: 74 µg/dl (control), 97 µg/dl (2 mg/kg/day), 116 µg/dl (4 mg/kg/day); digestion of crude protein, crude fiber, and crude fat unaffected by treatment	[74]
Zinc Carbonate	Rat/ Sprague-Dawley	n=5/group	1, 5, 10, 15, 35 mg/kg/day zinc supplied as Zinc Carbonate	Test substance administered in diet for 3 weeks; feces collection occurred last 3 days of experiment; animals killed at study termination; analysis for zinc content in organs and blood performed	Body weight and food intake statistically significantly lower in 1 mg/kg/day group because of zinc deficiency; zinc absorption on days 18-21 of study: 58% (1 mg/kg/day), 85% (5 mg/kg/day), 78% (10 mg/kg/day), 50% (15 mg/kg/day), 20% (35 mg/kg/day); study authors suggested that absorptive capacity of zinc is adaptive and greater in groups deficient or marginally deficient in zinc (1, 5, and 10 mg/kg/day groups); serum and kidney zinc concentrations increased from 1 mg/kg/day to 10 mg/kg/day groups, began to plateau at 15 mg/kg/day, and increased again at 35 mg/kg/day; pancreatic and femoral zinc concentrations increased linearly from 1 mg/kg/day to 15 mg/kg/day and began to level off at 35 mg/kg/day; zinc content in liver highest in 1 mg/kg/day group while other groups had substantially lower zinc content	[75]

Table 9. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Zinc Carbonate, Zinc Chloride, Zinc Chloride Hydroxide, all radiolabeled with ^{65}Zn	Rat/ Wistar	n=15 or 20/group	130 µg zinc supplied as Zinc Carbonate, Zinc Chloride, or Zinc Chloride Hydroxide	For 7 days prior to testing, animals administered a control diet (also containing 174 mg/kg ferrous sulphate); animals fasted overnight and administered single dose test substance in starch-sucrose paste on day 0; 6 hours post-dosing control diet administered and continued daily up through 14 days; feces collected from day 0 to day 4; radioactivity measured each day from day 0 (1 h post-dosing) through day 14	Body weight comparable for all three test groups during experiment; percent absorption of ^{65}Zn similar for Zinc Carbonate (48%), Zinc Chloride (45%), and Zinc Chloride Hydroxide (40%); fractional rate of ^{65}Zn loss/day reported as 0.0169, 0.0171, and 0.0158 for Zinc Carbonate, Zinc Chloride, and Zinc Chloride Hydroxide, respectively; study authors reported that fecal and carcass radioactivity over first 4 days accounted for administered radioactivity in all groups and suggested that no substantial zinc lost via urinary excretion	[42]
Zinc Chloride (radiolabeling on Zn)	Rat/ Wistar	n=30, males	0.1 µCi (3.7 kBq) of ^{65}Zn as Zinc Chloride (no further details provided)	Single dosage of test substance administered; no controls used; body fluids and tissues sampled 6 h and 24 h and 2, 4, 7, 14 days post-administration	Highest levels of zinc accumulated in small intestine, kidneys, liver, and large intestine; brain, prostate, heart, blood, skin, hairs and gonads contained small levels (accumulated concentrations not provided)	[8]
HUMAN						
Oral						
Zinc Acetate (unlabeled)	Human	n=5/sex	50 mg elemental zinc administered as Zinc Acetate	Two-way crossover, two-phase study design used; 7-day washout period between treatments; phase 1 subjects pretreated with single dose of 40 mg famotidine (intragastric pH ≥ 5) prior to administration of single dose test substance; phase 2 subjects were not pretreated (intragastric pH ≤ 3) prior to administration of single dose test substance; blood samples collected at time zero through 8 h post-administration; urine collected for 24 h post-administration	Absorption of zinc reported as mean plasma area under curve for Zinc Acetate was 524 µg/h/dL (intragastric pH ≤ 3) and 378 µg/h/dL (intragastric pH ≥ 5)	[13]

LOAEL = Lowest Observed Adverse Effect Level; NOAEL = No Observed Adverse Effect Level

Table 10. **Acute Toxicity Studies**

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
ANIMAL						
Dermal						
Zinc Stearate	Rabbit	n = Not specified	Not specified	Test substance applied to skin (no further details)	LD_{50} > 2000 mg/kg (no further details)	[53]
Zinc Sulfate (heptahydrate)	Rat/ Wistar	n = 5/sex	2000 mg/kg	Test substance applied semi-occlusively for 24 h using GLP in accordance with OECD TG 402 (Acute Dermal Toxicity); animals observed for 15 days post-application	LD_{50} > 2000 mg/kg; erythema (grades 1-2 of max grade 4) and scabs (scales 1-2 of max scale 3) in treated skin reported on days 2-8	[8,14,20]
Zinc Sulfide	Rat	Not specified	Not Specified	Not Specified	LD_{50} > 2000 mg/kg (No further details)	[76]
Oral						
Zinc Acetate (dihydrate)	Rat/ Wistar	n=5 males/group	Dosages in a logarithmic series varying by factor of 2 (water vehicle); no further details provided	Single dosage administered in accordance with OECD TG 423 (Acute Oral Toxicity); animals were non-fasted prior to dosing; use of controls not specified	Estimated LD_{50} of 2060 mg/kg reported for Zinc Acetate anhydrous; LD_{50} of 2460 mg/kg reported for Zinc Acetate (dihydrate)	[13]
Zinc Acetate (dihydrate)	Rat/ Sprague-Dawley	n=10, males	Not specified	Single dosage administered to animals; animals observed for 14 days	LD_{50} of 794 mg/kg Zinc Acetate (dihydrate) or 237 mg/kg zinc supplied as Zinc Acetate (dihydrate) reported	[77]
Zinc Acetate (dihydrate)	Mouse/ Swiss	n=10, males	Not specified	Single dosage administered to animals; animals observed for 14 days	LD_{50} of 287 mg/kg Zinc Acetate (dihydrate) or 86 mg/kg zinc supplied as Zinc Acetate (dihydrate) reported	[77]
Zinc Lactate	Rat/ Wistar	n=5/sex/group	500 or 2000 mg/kg (water vehicle)	Single dosage administered using GLP in accordance with OECD TG 401 (Acute Oral Toxicity); controls not used; animals observed for 14 days post-administration and then killed and examined	LD_{50} > 500 mg/kg and < 2000 mg/kg; 3 males and 5 females died 3 days following dosing with 2000 mg/kg; all animals in 500 mg/kg group survived; clinical signs reported were sluggishness, blepharospasm, piloerection, soiled fur; gross pathology exam revealed no treatment-related changes	[14]
Zinc Nitrate (hexahydrate)	Rat/ Sprague-Dawley	n=10, males	Not specified	Single dosage administered to animals; animals observed for 14 days	LD_{50} of 1330 mg/kg Zinc Nitrate (hexahydrate) or 293 mg/kg zinc supplied as Zinc Nitrate (hexahydrate) reported	[77]
Zinc Nitrate (hexahydrate)	Mouse/ Swiss	n=10, males	Not specified	Single dosage administered to animals; animals observed for 14 days	LD_{50} of 926 mg/kg Zinc Nitrate (hexahydrate) or 204 mg/kg zinc supplied as Zinc Nitrate (hexahydrate) reported	[77]
Zinc Phosphate	Rat/ Wistar	n=?	5000 mg/kg	Animals dosed in accordance with OECD TG 401	LD_{50} > 5000 mg/kg reported; no mortality or observed toxicity	[11]
Zinc Ricinoleate	Rat/ Wistar	n=5/sex/dosage	2000 mg/kg (water vehicle)	Animals dosed using GLP in accordance with OECD TG 401; animals observed 14 days post-dosing; animals killed after 14 days and examined; no controls used	LD_{50} > 2000 mg/kg reported; no toxicity or mortality observed; body weight gain normal; no treatment-related macroscopic observations during necropsy	[15]
Zinc Stearate	Rat	n=Not specified	Not specified	Procedures not provided	LD_{50} > 5000 mg/kg	[53]

Table 10. **Acute Toxicity Studies**

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
			Inhalation			
Zinc Chloride	Rat/ Sprague-Dawley	n=3 females/ group	600, 940, 1220, or 1950 mg Zn/m^3, supplied as Zinc Chloride (water vehicle)	Animals exposed to aerosol with MMAD of 2.3 µm for 10 min; animals observed for 7 days post-administration; necropsy performed	LC_{50} of 2000 mg/m^3 Zinc Chloride reported; no animals died in 600 mg/m^3 group; 1 animal per group died after exposure to 940 or 1220 mg/m^3; all animals died with 1950 mg/m^3 dosage; clinical signs observed were dyspnea, reduced locomotion, labored breathing, rhonci and rales; gross pathology revealed dark red lung surface, congestion, edema, and interstitial emphysema; histopathology showed atelectasis, hyperemia, hemorrhages, and edema in lungs	[14]
Zinc Stearate	Rat	n=10	Not specified	Animals exposed for 1 h	LC_{50} > 200,000 mg/m^3; 1 animal died in the 14-day observation period	[53]
Zinc Sulfate	Dog	n=5	0.1% (1.8 8.3 mg/m) and 1% (15.8 mg/m^3)	Anesthetized animals exposed to 0.1% aerosol (MMAD ~0.1 µm) for 7.5 min; lung volume and function measured prior to experiment and 5, 15, 30, 60, 120, 180 min post-exposure; animals then exposed to 1% submicron aerosol for 7.5 min; lung volume and function measured 5, 15, and 30 min post-exposure	Total respiratory resistance, static lung compliance, functional residual capacity, specific total respiratory conductance, and specific lung compliance not substantially affected by 0.1% and 1% treatment	[78]
Zinc Sulfate	Dog	n=5	0.5% (8.3 mg/m^3)	Anesthetized animals exposed to aerosol (MMAD ~0.1 µm) for 4 h; lung volume and function measured prior to experiment and each hour during and for 2 hours after exposure	Total respiratory resistance, functional residual capacity, static lung compliance, specific lung compliance, specific total respiratory conductance, mean pulmonary arterial and carotid arterial pressures, cardiac output, heart rate, stroke volume, arterial pH, and arterial O_2 and CO_2 tensions not substantially affected by treatment	[78]
Zinc Sulfate	Sheep	n=6	0.1% (1.8 mg/m^3)	Conscious animals exposed to aerosol (MMAD ~0.1 µm) for 20 min; tracheal mucous velocity measured at baseline and 30, 60, 120, and 180 min from beginning of exposure period	Tracheal mucous velocity not substantially affected by treatment	[78]
Zinc Sulfate	Sheep	n=5	0.5% (8.3 mg/m^3)	Conscious animals exposed to aerosol (MMAD ~0.1 µm) for 4 h; tracheal mucous velocity measured prior to and at end of experiment then again 2 h post-exposure	Tracheal mucous velocity not substantially affected by treatment	[78]

GLP = Good Laboratory Practice; LC_{50} = Lethal Concentration at which 50% of population dies; MMAD = Mass median aerodynamic diameter; OECD TG = Organization for Economic Co-operation and Development Test Guideline

Table 11. Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
ANIMAL							
Oral							
Zinc Acetate (dihydrate)	Rat/ Sprague-Dawley	n=10 females/ group	0, 160, 320, 640 mg/kg/day (sugar added to water vehicle for palatability)	3 mos	Animals dosed daily in drinking water in accordance with OECD TG 408 (Repeated Dose 90-Day Oral Toxicity in Rodents); negative controls received vehicle only	NOEL of 160 mg/kg/day for Zinc Acetate reported; 2 animals at 640 mg/kg/day level died; drinking water ingested and volume of urine excreted in 640 mg/kg/day group were lower than other treatment groups; food consumption, weight gain, feces excretion, and organ weights were unaffected by treatment at all dosage rates; hematocrit and hemoglobin levels unaffected by treatment; plasma urea and creatinine levels statistically significantly higher in 640 mg/kg/day group compared to controls; concentrations of zinc statistically significantly higher in liver, kidneys, heart, bone, and blood in 320 and 640 mg/kg/day groups compared to controls; zinc concentration in spleen statistically significantly higher compared to controls; severe histological lesions observed in kidneys in 640 mg/kg/day group	[13,79]
Zinc Sulfate (heptahydrate) (99.9% pure)	Mouse/ ICR and Rat/ Wistar	n=12 mice/sex/dosage; n=12 rats/sex/dosage	0, 300, 3000, 30,000 ppm	13 wks	Animals dosed daily in diet in accordance with OECD TG 408; negative controls used	*Mouse results*: NOEL of 3000 ppm (~458 mg/kg/day in males, ~479 mg/kg/day in females) reported; 4 animals died in 30,000 ppm group (33.3% mortality in males, 8.3% mortality in females); The following effects noted with 30,000 ppm treatment: depressed motility; histological analysis showed urinary tract impairment and exocrine gland regressive changes in pancreas; smaller body size; reduction in food intake during week 1 compared to controls; lower food efficiency compared to controls; decreased water consumption during week 1 which reversed in males but not in females; lower hematocrit and hemoglobin levels compared to controls; lower leukocyte level in males; morphological alterations in erythrocyte anisocytosis; polychroomatophilia and poikilocytosis in 6 males and 4 females with fore-stomach ulcers; decrease in total protein, glucose, and cholesterol and increase in alkaline phosphatase and urea nitrogen; abnormal liver enzyme levels; emaciation, ischemic discoloration of thyroid and kidney; pancreatic atrophy; thickening of small intestine; slight splenomegaly; relative and absolute organ weight fluctuations, but unclear if related to treatment; lesions in pancreas, intestine, stomach, spleen, kidney attributable to treatment; No treatment-related toxicity at ≤ 3000 ppm; slight, but reversible reduction in weight gain in females (300 ppm) after 1 week *Rat results*: NOEL of 3000 ppm; animals in groups fed < 3000 ppm displayed no signs of treatment-related effects; 2 females (control and 3000 ppm group) killed because of suppurative pyelitis; no deaths in 30,000 ppm group; reduced weight gain in males and slightly reduced weight gain in females (30,000 ppm); smaller body size (in males at 30,000 ppm); at 30,000 ppm reduction in food intake during week 3 (in males) and weeks 1-6 (in females); slight reduction in food efficiency and water intake at 30,000 ppm (males only); reduction in leukocyte count (30,000 ppm) and in males slight decrease in hematocrit and hemoglobin; females showed slight increase in hemoglobin (3000 ppm); reduced liver enzymes, reduced protein, cholesterol, and calcium (in males at 30,000ppm); reduced calcium (in females at 3000 ppm and 30,000 ppm); relative and	[10,80]

Table 11. Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
						absolute organ weight fluctuations, but unclear if treatment-related; treatment-related pancreatic lesions observed (30,000 ppm)	
				Inhalation			
Zinc Sulfate (heptahydrate)	Rat/ Wistar Kyoto	n=12/group	Filtered air or 10, 30, or 100 µg/m^3 water soluble Zinc Sulfate (particle size 30-43 nm)	16 wks	Test substance administered through nose inhalation for 5 h/day for 3 days/wk; necropsy performed 48 h following final exposure; analysis of plasma/serum, cardiac RNA and cardiac mitochondria isolation, pathology of lung and heart, and broncho-alveolar lavage fluid analysis performed	Neutrophil and macrophage count, lavageable cells, and enzyme activity in bronchoalveolar lavage fluid not substantially changed by treatment; reduction in cytosolic glutathione peroxidase activity and succinate dehydrogenase activity and increase in levels of mitochondrial ferritin in heart; cell signaling genes revealed small changes (100 µg/m^3) detected in gene array analysis test; plasma/serum markers unaffected bytreatment; pathology revealed no pulmonary or cardiac changes as a result of treatment	[81]
				HUMAN			
				Oral			
Zinc Acetate	Human	n=103 total (age 60-89 years) healthy subjects; n=36 in placebo group; n=36 in 15 mg/day group; n=31 in 100 mg/day group	0, 15, 100 mg/day zinc supplied as Zinc Acetate	3 mos	Treatment orally administered with evening meal in double-blind study; subjects also administered (with breakfast) vitamin-mineral supplements not containing zinc; blood samples collected initially and after 3 months; assay performed using standard techniques to evaluate proliferative response to mitogens/antigens	Zinc concentrations in plasma statistically significantly higher in 100 mg/day group (28% increase compared to initial value) but not in 15 mg/day and placebo groups; cellular zinc concentrations, serum cholesterol, serum HDL cholesterol, serum alkaline phosphatase, and serum albumin unaffected by treatment; lymphocyte proliferative responses to mitogens/antigens unaffected by Zinc Acetate treatment, but 14 of 15 subjects with initially reduced lymphocyte proliferative response improved (study authors attributed this potentially to vitamin-mineral supplements)	[82]

NOAEL = No-Observed-Adverse-Effect-Level; NOEL = No-Observed-Effect-Level; OECD TG = Organization for Economic Co-operation and Development Test Guideline

Table 12. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Zinc Acetate	Mouse/ BALB/c	n= 30/group (sex distribution not specified)	500 or 1000 mg/l (water vehicle)	Test substance administered in drinking water beginning from day of mating through gestation, lactation, and post-weaning; vehicle controls used; humoral immunity test performed (mice injected with 0.5 ml of 15% sheep erythrocytes and killed after 5 days, spleen extracted and assayed for IgM and IgG producing cells); specific cell-mediated immunity test performed to examine mitogen-induced proliferation	LOAEL of 136 mg/kg/day zinc reported for male and female mice because mice exposed in utero continuing postnatally showed direct plaque-forming activity of spleen cells increase as did lymphocyte proliferation with mitogen stimulation; no clinical signs, mortality, body weight changes, food consumption, or gross pathological findings related to treatment observed; treatment-related hematological and clinical biochemistry findings observed, but no further details provided	[13]
Zinc Chloride (99.99% purity)	Rat/ Sprague-Dawley	n=25/sex/group	0, 7.5, 15, 30 mg/kg/day (water vehicle)	Test substance administered daily by gavage in accordance with OECD TG 416 (Two-Generation Reproduction Toxicity Study); animals dosed for 77 days before cohabitation, during cohabitation (21 days), and during gestation (21 days) and lactation (21 days) in females; controls dosed with vehicle only	F1 generation overall NOAEL of 7.5 mg/kg/day reported; parental animals from F0 and F1 generations showed reduced fertility and viability; reduced body weight of F1 and F2 pups in 30 mg/kg/day group, however no effects on weaning index, sex ratio, or litter size observed; F0 and F1 parental males and postpartum dams (F0 and F1) showed reduced body weight; reduced weights of brain, liver, kidney, spleen and seminal vesicles in F0 males and reduced weight of spleen and uterus of F0 females; reduced weights of brain, liver, kidney, adrenal, spleen, prostate and seminal vesicles of F1 males and reduced spleen and uterus of F1 females; no change in clinical signs or clinical pathology in F0 and F1 parental rats, but alkaline phosphatase levels increased for F0 and F1 males and females; parental rats in both generations showed gross lesions in gastro-intestinal tract, lymphoreticular/ hematopoietic and reproductive tract; F1 parental rats had reduced body fat; F1 male mortality rate of 0, 12, 8, and 4% and F1 female mortality rate of 0, 8, 12, and 20% reported for control, 7.5, 15, and 30 mg/kg/day groups, respectively	[14,84]
Zinc Chloride (99.99% pure)	Rat/ Sprague-Dawley	n=25/group	0, 7.5, 15, 30 mg/kg/day (water vehicle)	Test substance administered daily by gavage; males and females dosed for 84 days through premating and mating (14 days), and during gestation (21 days) and lactation (21 days) in females; controls dosed with vehicle only	Difficulty in handling was main clinical sign reported at all treatment levels; implantation efficiency statistically significantly reduced in 7.5 mg/kg/day treated females; statistically significant increase in stillbirths (15 and 30 mg/kg/day); statistically significant decrease in pups per litter in all treated groups compared to controls; dose-dependent increase in birth mortality in treated animals; in treated (all levels) males statistically significant reduction in food consumption at varying time-points compared to controls; female body weight unaffected by treatment during premating phase, but males had statistically significant reduction in body weight (15 and 30 mg/kg/day groups) compared to controls in premating period; treated females showed statistically significant reduction in body weight	[83]

Table 12. **Developmental and Reproductive Toxicity (DART) Studies**

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
					during mating (30 mg/kg/day), gestation (15 and 30 mg/kg/day), and lactation (all treatment levels); statistically significant reduction in feed consumption (various treatment levels) during pregnancy and last week of lactation; food conversion ratio statistically significantly lower during pregnancy (all treatment levels), but unaffected during lactation; in treated females (various levels) relative weight ratios of kidney, pancreas, liver, brain, and uterus statistically significantly higher; in treated males (various levels) relative weight ratios of brain, liver, and testes statistically significantly increased while weight ratio of seminal vesicles and kidney statistically significantly decreased; no histopathological lesions found in treated males or females; in treated males and females (various levels) serum clinical chemistry parameters statistically significantly different than controls; white blood cell counts statistically significantly increased in treated females (15 and 30 mg/kg/day); male pups born to treated females (30 mg/kg/day) exhibited statistically significantly longer anogenital distance (female pups unaffected); male and female pups born to treated females (various levels) showed statistically significantly earlier incisor eruption and eye opening versus controls	
Zinc Sulfate	Rat/ Wistar	n=25/group	0, 0.4, 2.0, 9.1, 42.5 mg/kg (water vehicle)	Pregnant, female rats dosed by gavage on days 6-15 of gestation; necropsy performed day 20; positive and negative controls used; skeletal and soft tissue examinations of fetuses performed	Maternal and developmental NOEL of 42.5 mg/kg (~17 mg/kg zinc equivalent) reported; no treatment-related effects observed	[85]
Zinc Sulfate	Rabbit/ Dutch	n=14-19/group	0, 0.6, 2.8, 13.0, 60.0 mg/kg (water vehicle)	Pregnant, female rats dosed by gavage on days 6-18 of gestation; necropsy performed day 29; positive and negative controls used; skeletal and soft tissue examinations of fetuses performed	Maternal and developmental NOEL of 60.0 mg/kg (~24 mg/kg zinc equivalent) reported; no treatment-related effects observed; positive controls performed as expected	[85]
Zinc Sulfate (unspecified as to whether the anhydrous form or heptaphydrate was used)	Hamster	n=23-25/group	0.9, 4.1, 19 and 88 mg/kg/day	Animals dosed by gavage on days 6-10 of gestation; negative controls were used; females killed on day 14	Maternal and fetal NOAEL of 88 mg/kg/day (35.2 mg or 19.9 mg Zn^{2+}/kg for anhydrous form or heptahydrate, respectively) reported	[9,20]
Zinc Sulfate (anhydrous)	Rat/ Charles-Foster	n=18/sex/dose (treatment group); n=15/sex/dose (control group)	4000 ppm zinc supplied as Zinc Sulfate (males only)	Males dosed daily in diet as indicated for 30-32 days then mated with untreated females; males killed after mating and sperm collected immediately to evaluate motility/viability, reproductive organs dissected; females had full-term gestation and were not killed; controls fed plain diet	All control females conceived, but only 11 of 18 females mated with treated males conceived; statistically significantly lower number of live births/ mated female in treatment group compared to controls; significantly significant increase in zinc content in testis and sperm of treated males compared to controls; statistically significant decrease in sperm motility, measured 30 min to 4 h, from treated males compared to controls; sperm	[10,86]

Table 12. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
					vitality at 4 h not statistically significantly different in treated males compared to controls; no clinical signs, malformed litters, or stillbirths observed in pups from treatment or control groups	
Zinc Sulfate (anhydrous)	Rat/ Charles-Foster	Test 1: n=15 females/group; Test 2: n=18 females/group	12 (controls) or 4000 ppm zinc supplied as Zinc Sulfate	Test 1 (post-coitum supplementation): Test substance added to diet of females on first day of conception through study termination; females killed on gestation day 18; negative controls used (12 ppm zinc content in regular, unsupplemented diet) Test 2 (pre- and post-coitum supplementation): Test substance added to diet of females 21 to 26 days prior to mating through study termination; females killed on gestation day 18; negative controls used (12 ppm zinc content in regular, unsupplemented diet)	Test 1: statistically significant decrease in number of conceptions of treated (5 conception out of 12 mated females) comparted to control (12 conceptions out of 12 mated females) animals; lower number of implantation sites per pregnant female in treated (5) compared to controls (7), but not statistically significant; resorption sites in controls (2) similar to treated (1) animals; mean placental and fetal weights unaffected by treatment; no stillbirths or malformed fetuses Test 2: no statistically significant difference in number of conceptions in controls (10 out of 11 mated females conceived) compared to treated animals (14 out of 15 mated females conceived); no difference of implantation sites per pregnant female in controls compared to treated animals; resorption sites in controls (4) similar to treated (6) animals; mean placental and fetal weights unaffected by treatment; no stillbirths or malformed fetuses	[87]
Zinc Sulfate	Mouse/CD-1	n=25-30 animals/ group	0.3, 1.4, 6.5, and 30 mg/kg/day (30 mg/kg/day group equivalent to 12 mg or 6.8 mg Zn^{2+}/kg for anhydrate or heptahydrate, respectively)	Females dosed by gavage on days 6-15 of gestation; controls used; females killed on day 17 of gestation	Maternal and fetal NOAEL of 30 mg/kg/day reported; maternal body weight, maternal survival, number of corpora lutea, implantations and resorptions unaffected by treatment; live litters, fetus weights, fetus deaths, and sex ratio unaffected by treatment; no difference in soft or skeletal tissue abnormalities between treated and control groups	[10]

LOAEL = Lowest-Observed-Adverse-Effect-Level; NOAEL = No-Observed-Adverse-Effect-Level; NOEL = No-Observed-Effect-Level; OECD TG = Organization for Economic Co-operation and Development Test Guideline

Table 13. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
			IN VITRO		
Zinc Acetate	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100	50 to 7200 µg/plate	Ames test conducted with and without metabolic activation	Negative	[88]
Zinc Acetate	Mouse lymphoma cells (L5178Y)	1.3, 1.8, 2.4, 3.2, 4.2, 5.6, 7.5, 10, 13 µg/ml without metabolic activation; 4.2, 5.6, 7.5, 10, 13, 18, 24, 32, 42 µg/ml with metabolic activation	Mouse lymphoma assay (TK+/-) performed with and without metabolic activation; negative and positive controls used	Positive (dose-dependent) results both with and without metabolic activation; at 10 µg/ml, both with and without metabolic activation, mutation frequency doubled; controls performed as expected	[88]
Zinc Acetate	Chinese hamster ovary cells	25, 34, 45 µg/ml without metabolic activation; 45, 60, 80 µg/ml with metabolic activation	Chromosomal aberrations assay performed both with and without metabolic activation	Positive (dose-dependent) responses both with and without metabolic activation; controls performed as expected	[88]
Zinc Acetate	Rat hepatocytes	10 to 1000 µg/ml	Unscheduled DNA synthesis test conducted	Negative	[88]
Zinc Acetate	Human lymphocytes	1 x 10^{-3}, 1 x 10^{-4}, 1 x 10^{-5}, 1 x 10^{-6}, 1 x 10^{-7} M zinc supplied as Zinc Acetate	1 ml of venous blood from healthy, male donor exposed to Zinc Acetate for 3 h at 37 °C; 200 cells containing complete chromosome complement assayed for 48 h at each concentration to detect structural chromosome gaps and aberrations; untreated controls used	No statistically significant gaps observed for treated compared to control samples	[89]
Zinc Acetate, Zinc Chloride, Zinc Sulfate	Human leucocytes	1.5 x 10^{-3}, 3.0 x 10^{-4}, 3.0 x 10^{-5}M zinc supplied as Zinc Acetate, Zinc Chloride, Zinc Sulfate (distilled water vehicle for Zinc Chloride and Zinc Sulfate; dimethyl sulfoxide vehicle for Zinc Acetate)	Clastogenicity experiment performed in separate cultures for each test substance or vehicle controls; inoculation occurred at 0 and 24 h; cultures harvested 48 and 72 h following initiation; cultures prepared for evaluation of chromosomal aberrations	Highest concentrations lethal for all three test substances; 3.0 x 10^{-4} and 3.0 x 10^{-5}M concentrations showed statistically significant increase in chromosomal aberrations compared to controls for all test substances; generally chromosomal aberrations higher in 72 h cultures for all test substances	[51]
Zinc Chloride	Mouse L5178Y/$TK^{+/-}$ lymphoma cells	1.21 to 12.13 µg/ml in normal saline followed by filter sterilization	Cells were directly exposed to test substance for 3 h in L5178Y $TK^{+/-}$ to $TK^{-/-}$ point-mutation assay; solvent controls used	Non-mutagenic; test substance did not induce trifluorothymidine-resistant mutants	[91]
Zinc Chloride (99.9% pure)	Human dental pulp cells (D824 cells)	30, 100, 300 µM	Chromosomal aberrations assay performed without metabolic activation; cells treated for 3 or 30 h; negative controls used; an additional experiment performed using same concentrations of treated cells with metabolic activation (negative controls and positive controls used)	Treated cells, both with and without metabolic activation, negative for chromosomal aberrations; controls performed as expected	[69]

Table 13. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Zinc Chloride	Human peripheral blood leucocytes	1.5 x 10^{-3}, 3.0 x 10^{-4}, 3.0 x 10^{-5}M zinc supplied as Zinc Chloride	Clastogenicity experiment performed; inoculation occurred at 0 and 24 h; cultures harvested 48 and 72 h following initiation; cultures prepared for evaluation of mitotic index and chromosomal aberrations; distilled water controls used	Study researchers found excess zinc to be clastogenic and mitostatic (1.5 x 10^{-3}M lethal at 48 and 72 h); statistically significant increase in chromosomal aberrations at 48 and 72 h with both 0 and 24 h inoculation periods for 3.0 x 10^{-4} and 3.0 x 10^{-5}M compared to controls; statistically significant decrease in mitotic index value at 48 and 72 h with both 0 and 24 h inoculation periods for 3.0 x 10^{-4} and 3.0 x 10^{-5}M compared to controls	92
Zinc Chloride	*S. typhimurium* TA98, TA100	1, 10, 25, 100 mg/l with metabolic activation 1, 10, 25 mg/l without metabolic activation (100 mg/l cytotoxic without metabolic activation) (water vehicle)	Ames test performed with and without metabolic activation as indicated; positive and negative controls used	Non-mutagenic; controls performed as expected	90
Zinc Chloride	Human peripheral blood lymphocytes	1, 10, 100 mg/l (water vehicle)	Micronucleus assay conducted; cell proliferation kinetics (mitotic index) test also performed; negative controls used for both experiments	Genotoxicity observed at 100 mg/l in micronucleus assay (micronuclei statistically significantly higher than negative controls); cytotoxicity noted at 100 mg/l; micronuclei counts higher than negative control at 1 and 10 mg/l, but not statistically significant; controls performed as expected; mitotic activity decreased with increasing concentration (statistically significant at 100 mg/l after 48 h exposure compared to controls); cytotoxicity noted at 100 mg/l	90
Zinc Chloride	Human leucocytes	1.5 x 10^{-4} and 3.0 x 10^{-4}M zinc supplied as Zinc Chloride (deionized water vehicle)	Cytokinesis-block micronucleus assay performed to determine if test substances induced micronucleus formation; each test substance added to separate cell cultures 24 h following initiation; at 72 h cultures terminated; positive and vehicle controls used	Statistically significant increase in micronucleated cytokinesis- blocked cells in treated (both concentrations, however, not dose-dependent) compared to vehicle control cells	93
Zinc Chloride	*Escherichia coli* WP2	3.2 mM	Experiment conducted to determine if test substance caused DNA damage and induced a pleiotropic response in *E. coli*; test substance exposure was 20 h; vehicle, negative, and positive controls used	Test substance caused 2-fold increase in λ prophage induction compared to controls; controls performed as expected	14
Zinc Chloride	Human lymphocyte cultures	0, 0.003M, 0.0003M or 0.00003M	0.003M used to evaluate cytotoxicity; 0.0003M or 0.00003M test substance added to 48-h (first cell division) and 72-h (second cell division) cultures of human lymphocytes from healthy donor at time zero and 24 h following initiation; negative controls used; metaphases from cultures assayed for aberrations (numerical and structural); 100 cells analyzed for each treatment or control group	Mytotic activity inhibited at 0.003M; Control results (48 h culture): 3 aneuploid cells, 0 cells in endoreduplication, 1 gap chromatid aberrations; 0.0003M results at time zero (48 h culture): 1 aneuploid cells, 0 cells in endoreduplication, 2 gap chromatid aberrations; 0.0003M results at 24 h post-initiation (48 h culture): 4 aneuploid cells, 0 cells in endoreduplication, 2 gap chromatid aberrations, 2 fragment chromosome aberrations; 0.00003M results at time zero (48 h culture): 4 aneuploid cells, 0 cells in endoreduplication, 3 gap chromatid aberrations, 1 dicentric chromosome aberrations; 0.00003M results at 24 h post-initiation (48 h culture): 4 aneuploid cells, 2 gap chromatid aberrations, 2 fragment	169

Table 13. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
				chromosome aberrations; Control results (72 h culture): 2 aneuploid cells, 0 cells in endoreduplication, 3 gap chromatid aberrations; 0.0003M results at time zero (72 h culture): 3 aneuploid cells, 0 cells in endoreduplication, 0 structural aberrations; 0.0003M results at 24 h post-initiation (72 h culture): 6 aneuploid cells, 0 cells in endoreduplication, 3 gap chromatid aberrations, 1 fragment chromosome aberrations; 0.00003M at time zero (72 h culture): 4 aneuploid cells, 0 cells in endoreduplication, 3 gap chromatid aberrations, 2 dicentric chromosome aberrations 0.00003M at 24 h post-initiation (72 h culture): 2 aneuploid cells, 1 cell in endoreduplication, 2 gap chromatid aberrations, 1gap chromosome aberrations	
Zinc Chloride	*S. typhimurium* TA97	0, 15.62, 31.25, 62.50, 125, 250.5, 500, 1000 µM/plate for preincubation tests without inhibitor; 18.75, 37.5, 75, 150, 300 µM/plate for preincubation tests with inhibitor; 0, 75, 150, 200, 300 µM/plate for tests using individual Vogel Bonner minimal medium salts (vehicle=distilled, deionized water)	Ames test conducted; various preincubation mixtures were evaluated including water (distilled, deionized), sodium phosphate buffer (0.1 M, pH 7), or HEPES buffer in sodium and potassium chloride (0.1 M, pH 7); solvent controls used; in preincubation tests 500 µl water or buffer, 50 µl test substance, and 100 µl cell culture added to tubes and incubated at 37 °C for 30 min; then top agar added to tubes, mixed, and plated on agar plates; 44 to 48 h after incubation His^+ colonies scored; another set of tests using inhibitor diethyldithiocarbamate (chelator) were conducted; 50 µl inhibitor was added to preincubation test tube mixture following addition of cell culture and assayed similarly as above; agar contained Vogel Bonner minimal medium with salts including $MgSO_4$, $NaNH_4HPO_4$,K_2HPO_4, and citrate (pH 4.5); tests conducted to evaluate effect of individual salts' ability to inhibit mutagenesis of test substance; salt component (controls without salt also used) added after cell culture and assayed similarly as above; HEPES buffer system used	Zinc mutagenic in the distilled, deionized water or HEPES buffer systems used in preincubation test conditions; at 1000 µM/plate in the HEPES buffer system toxicity noted as no microcolonies observed; no mutagenesis attributed to zinc observed in phosphate buffer system; diethyldithiocarbamate inhibited mutagenesis of zinc; all 4 salts tested inhibited mutagenesis of zinc to some extent compared to mutagenicity of zinc observed in controls with no salt added	[170]
Zinc Nitrate (hexahydrate)	*S.typhimurium* TA98, TA100	0.01 mM and 1 mM	Ames test performed with and without metabolic activation (S9 mix)	Negative	[94]
Zinc Stearate	*S.typhimurium* TA1535, TA1537, TA98, TA100; *Saccharomyces cerevisiae* strain 04	Range of test concentrations used based on 50% survival value, however concentrations used not specified (dimethylsulfoxide, water, or saline vehicles)	A bacterial reverse mutation assay was performed with and without metabolic activation; water, saline, and positive controls used	Non-mutagenic	[16]

Table 13. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Zinc Sulfate	*S. typhimurium* TA1535, TA1537, TA98, TA100, TA1538	5 concentrations up to 3600 µg/plate (no further details provided)	Ames test conducted both with and without metabolic activation; solvent and negative controls not used; positive controls used	Non-mutagenic; positive controls performed as expected	[10]
Zinc Sulfate	*S. cerevisiae* diploid strain D4	5000/ 1000 ppm (vehicle 0.1 M potassium phosphate buffer, pH 7.5)	Mitotic recombination assay performed with 4-h exposure duration; gene conversion evaluated at ade2 and trp5 loci; solvent controls used	Non-convertogenic	[17]
			IN VIVO		
Zinc Chloride	Mouse/ C57B1; n=25/group	0.5% zinc supplied as Zinc Chloride	For 1 month animals fed standard diet, which included 1.1% calcium, or diet low in calcium (0.03%); test substance was added to each type of diet; controls were administered a normal or low-calcium diet without test substance; at study termination 10 animals killed for assay	Statistically significant decrease in body weight for treated animals on either the standard or low-calcium diet compared to their respective controls; treated animals on standard diet had statistically significantly lower serum calcium than controls on standard diet; treated animals on low-calcium diet had statistically significant increase in chromosomal aberrations compared to controls on low-calcium diet	[171]
Zinc Chloride	Mouse/ Swiss albino; n = 5/group	7.5, 10, 15 mg/kg	Single dosage administered intraperitoneally; mice killed 24 h post-administration; negative and positive controls used; control animals killed 24 h post-administration	Statistically significant, dose dependent increase in chromosomal aberrations of bone-marrow cells in treatment (at all levels tested) compared to control animals	[95]
Zinc Chloride	Mouse/ Swiss albino; n = 5/group	7.5, 10, 15 mg/kg	Dosage administered daily for 5 days, same dosage was used each day for each test group; negative and positive controls used; control animals killed 24 h post-administration	Statistically significant, dose-dependent increase in sperm-head abnormalities in treated animals compared to controls	[95]
Zinc Chloride	Mouse/ Swiss albino; n = 5/group	2.0, 3.0 mg/kg	Dosage administered on alternate days; animals killed on days 8, 16, and 24; negative and positive controls used; control animals killed 24 h post-administration	Statistically significant, dose-dependent increase in chromosomal aberrations of bone-marrow cells in treatment (at all levels tested) compared to control animals	[95]
Zinc Sulfate	Mouse/ Swiss albino, n=6 males/group	0, 5.7, 8.55, 11.40, 14.25, 17.10, 19.95 mg/kg (distilled water vehicle)	Animals orally dosed; Comet assay performed (alkaline single cell gel electrophoresis) to detect single strand DNA breaks (damaged DNA resembles a comet and normal DNA resembles a halo); blood samples collected 24, 48, 72, 96 h and during first week following treatment; negative (distilled water) and positive (25 mg/kg cyclophosphamide administered intraperitoneally) controls used; DNA damaged quantified by comment tail-length	Statistically significant dose-dependent DNA damage seen in treated compared to control animals; DNA damage gradually decreased (comet tail-length decreased) at 48 h and beyond for each dosage level; DNA comet tail-length in all treated groups similar to controls by 1 week post-treatment; cell viability confirmed at each dosage level and time point; no treatment-related deaths reported	[96]

HEPES buffer = (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), zwitterionic biological buffer pH 6.8-8.2[172]

Table 14. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration (Vehicle)	Procedure	Results	Reference
IRRITATION						
Animal						
Zinc Acetate, Zinc Chloride, Zinc Sulfate, Zinc Undecylenate (purity of above zinc salts ≥ 98%)	Mouse/ TO, AG2; Rabbit/ New Zealand White; Guinea Pig/ Dunkin-Hartley white	n=6 mice/ group; n=4 male rabbits/test; n=6 guinea pigs	Group 1: 20% (w/v) Zinc Acetate (deionized water vehicle); Group 2: 1% (w/v) Zinc Chloride (deionized water vehicle); Group 3: 1% (w/v) Zinc Sulfate (deionized water); Group 4: 20% (w/v) Zinc Undecylenate (0.1% Tween 80 vehicle) Controls treated with deionized water (Group 5) or Tween 80 (Group 6)	In all animals skin shaved (5 cm^2 patch) in mid-dorsal areas (skin cleaned with 70% alcohol prior to application of test substance); Mouse test: 0.5 ml of each test substance or control (groups 1-6) applied to skin site for 5 consecutive days in open patch test (animals anaesthetized while treatment dried); 24 h after 5th treatment day animals killed Rabbit tests: Test 1-0.5 ml of each test substance or control (groups 1-6) applied to skin sites on either side of mid-dorsal line (6 treatment sites per rabbit) for 5 consecutive days in open patch test (animals restrained while treatment dried); 24 h after 5th treatment day animals killed Test 2-0.5 ml of each test substance or control (groups 1-6) applied to sterile gauze and secured to skin sites on either side of mid-dorsal line (6 treatment sites per rabbit) with occlusive covering for 3 days; 3 days post-application coverings removed to examine skin and 2 animals killed; treatment re-applied as above to 2 remaining animals for 2 more days and then coverings removed to examine skin and animals killed Guinea Pig test: test substance or controls applied to skin sites (1 test substance group or control group in 3 replicates per animal) for 5 consecutive days in open patch test (animals restrained while treatment dried); 24 h after 5th treatment day animals killed Histology (all animals) and epidermal cell kinetics (mouse only) performed	Zinc Acetate: severely irritating in rabbit (occlusive patch test); irritating in mouse; slightly irritating in rabbit (open patch test); non-irritating in guinea pig Zinc Chloride: severely irritating in both rabbit tests and mouse; irritating in guinea pig Zinc Sulfate: slightly irritating in both rabbit tests, mouse, and guinea pig Zinc Undecylenate: slightly irritating in both rabbit tests and mouse; non-irritating in guinea pig Controls: non-irritating in all animals Histology revealed zinc from Zinc Acetate, Zinc Chloride, and Zinc Sulfate (less frequently) detected in superficial skin layers (bound to epidermal keratin) of all animals Epidermal cell kinetics test showed Zinc Acetate and Zinc Chloride induced epidermal hyperplasia; Zinc Sulfate and Zinc Undecylenate performed similarly to controls	[103]
Zinc Chloride	Mouse/ SKH1	n=4	30% solution (vehicle not specified)	Test substance applied 1 x/day for 5 days to dorsal skin; non-invasive mexametry using multiprobe adapter system utilized for erythema evaluation	Dry skin and erythema reported	[173]
Zinc Chloride (98% pure)	Mouse/ TO (outbred)	n=6 males/group	1% w/v Zinc Chloride solution, pH 5.6 (deionized water vehicle)	0.5 ml test substance applied to 5x5 cm^2 clipped skin area (open test conditions) for 5 consecutive days; controls received vehicle only; animals killed 24 h following last application; histology on treated and control skin samples performed; skin samples stained with morin dye to evaluate zinc epidermal keratin binding	Severe skin irritation reported in all treated animals by 5 days; epidermal hyperplasia (ulceration and parakeratosis) observed in treated animals; zinc highly bound to epidermal keratin; no reactions noted in controls	[8]

Table 14. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration (Vehicle)	Procedure	Results	Reference
Zinc Chloride (98% purity)	Rabbit/ New Zealand White	n=4/ test	1% w/v Zinc Chloride solution, pH 5.6 (deionized water vehicle)	*Open patch test performed*: 0.5 ml test substance applied to 5 x 5cm^2 shaved skin for 5 consecutive days in open patch test; skin treated with vehicle only on other side of mid-dorsal line served as control; skin observed during and after test period; animals killed on day 6 *Occlusive patch test performed*: 0.5 ml test substance applied to 5 x 5 cm^2 shaved skin and covered with occlusive patch for 3 days; patch removed and skin examined 3 days post-application and 2 animals killed; test substance re-applied to remaining animals and occlusively covered for 2 more days, then those animals were killed; skin from test animals evaluated for histology	Severely irritating in both open and occlusive patch tests; no reactions in controls; epidermal hyperplasia with ulceration and parakeratosis seen in open patch test, which were also noted in occlusive patch test, but more severely; study authors indicated zinc highly bound to epidermal keratin	[19]
Zinc Lactate	Rabbit/ New Zealand White	n=3 males	Solid crystalline (unchanged), water used in application to ensure good skin contact with test substance	0.5 g test substance applied to 6 cm^2 area of shaved animal skin and covered with occlusive patch for 4 h using GLP in accordance with OECD TG 404 (Acute Dermal Irritation/ Corrosion); untreated skin used as control; after 4 h patch removed and skin washed with water to remove test substance; skin examined at 1, 24, 48, and 72 h following patch removal	Non-irritating	[14]
Zinc Neodecanoate	Rabbit/ Himalayan	n=3	Undiluted	0.5 ml test substance applied to 6cm^2 shaved, intact skin area and covered semi-occlusively for 4 h using GLP in accordance with OECD TG 404; animals examined 1, 24, 48, and 72 h post-application; untreated skin used as control	Non-irritating; no skin reactions observed	[18]
Zinc Nitrate (hexahydrate)	Rabbits, Guinea Pigs, Rats	n=?	Concentration not specified	Single application (no further details provided)	At 1 and 16 h post-application pronounced skin irritation reported (no further details provided)	[22]
Zinc Ricinoleate	Rabbit/ New Zealand White	n=6	Solid powder (undiluted, no vehicle)	0.5 g test substance applied to 2.5 cm^2 shaved (right side intact and left side abraded) animal skin and covered with occlusive patch for 4 h using GLP in accordance with OECD TG 404; untreated skin used as control; after 4 h patch removed and skin washed with water to remove test substance; skin examined 4, 24, 48, and 72 h post-application	Non-irritating; no skin reactions observed	[15]
Zinc Sulfate	Rabbit/ New Zealand White	n=3	Zinc Sulfate, moistened, but no vehicle used (no further details provided)	0.5 g test substance applied to shaved animal skin and covered, semi-occlusively, for 4 h in accordance with OECD TG 404; patch removed and skin examined at 1, 24, 48, and 72 h post-application (no further details provided)	Non-irritating; no signs of toxicity	[20]
				Human		
Zinc Sulfide	Human	n=not specified	Concentration not specified	Procedure not provided	Non-irritating (no further details provided)	[21]
Zinc Stearate	Human	n=not specified	10%	2 eye shadows tested (no further details)	Non-irritating (no further details provided)	[53]

Table 14. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
SENSITIZATION						
Animal						
Zinc Sulfate	Mouse/ BALB/c	n=3 females	10% solution (vehicle = 20% ethanol solution)	LLNA performed by applying 25 µl test substance to dorsum of both ears (abraded) for 3 days; draining lymph nodes excised on day 4; lymph node single cell suspension prepared and evaluated; vehicle controls used	Non-sensitizing; stimulation index reported to be 1.41 (stimulation index ≥ 3 is positive response)	[14,104]
Zinc Sulfate	Guinea Pig	n = 10 treated; n = 5 controls	Intradermal induction: 0.1% Epidermal induction: 50% Challenge: 50% (pre-treatment with 10% sodium dodecylsulfate)	Maximization test performed in accordance with OECD TG 406 (no further details provided)	After first challenge treatment, weak reactions reported in 5 of 10 treated animals and 2 of 5 control animals; following second challenge, reactions noted in 4 of 10 treated animals and 2 of 5 controls	[53]
Human						
Zinc Stearate	Human	n=202	10% in eye shadow formulation	Prospective patch test performed (Schwartz-Speck method)	Non-sensitizing	[53]
Zinc Stearate	Human	n=99	10% in eye shadow formulation	HRIPT conducted (Draize-Shelanski method)	Non-sensitizing	[53]

EU = European Union; GLP = Good Laboratory Practice; HRIPT = Human Repeat Insult Patch Test; LLNA = Local Lymph Node Assay; non-GLP = non-Good Laboratory Practice; OECD TG = Organization for Economic Co-operation and Development Test Guideline

Table 15. Ocular Irritation

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
IN VITRO						
Zinc Acetate (97%)	Chicken	n=3 eyeballs/group	0.03 g (no vehicle)	Enucleated eyeballs incubated for 45-60 min at 32 °C with physiological saline prior to treatment; test substance applied to corneas for 10 seconds followed by 20 ml saline rinse; method followed GLP in accordance with OECD TG 438 (Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants); observations made 30, 75, 180, and 240 min post-treatment rinse; negative and positive controls used	Defects and partial lesion (of anterior epithelium) in treated corneas reported; Bowman's membrane showed separating layers in treated corneas; study author's reported irreversible effects on eye causing eye corrosion/irritation; controls performed as expected	[13]
Zinc Citrate	N/A	Human corneal tissue (three-dimensional model)	Particulate powder (no vehicle)	50.4 mg test substance applied to tissue for 6 h using GLP in accordance with OECD TG 492 (Reconstructed Human Cornea-like Epithelium Test Method for Identifying Chemicals Not Requiring Classification and Labelling for Eye Irritation or Serious Eye Damage); negative and positive controls used	Test substance considered eye irritant; relative absorbance values of 4.7% reported (threshold for eye irritation potential ≤ 60%)	[12]
IN VIVO						
Zinc Lactate	Rabbit/ New Zealand White	n=3	Solid powder (unchanged, no vehicle)	0.1 g test substance instilled into lower right formix of conjunctiva using GLP in accordance with OECD TG 405; eyes unrinsed following application of test substance; untreated eye used as control; animals observed 7 days post-application	Very irritating; conjunctival damage not completely reversible by 7 days in all 3 animals; severe corneal lesions not completely reversible in 2 animals by 7 days; iris congestion and chemosis not fully reversible in 2 animals by 7 days	[14]
Zinc Nitrate (hexahydrate)	Rabbit	n=?	Concentration not specified	Procedures not provided	Irritating; study author's reported dimness of cornea, mucous membrane ulceration, and cicadricial alterations in eyelids	[22]
Zinc Phosphate	Rabbit/ New Zealand White	n=3	100 mg (no vehicle)	Test substance instilled into conjunctival sac of left eye using GLP in accordance with OECD TG 405; other eye served as untreated control; eyes (unrinsed) examined at 1, 24, 48, and 72 h post-application	Non-irritating; in 2 animals slight irritation of conjuctivae and chemosis noted within 48 h post-application; no iris or corneal lesions or conjunctival discharge observed	[11]
Zinc Ricinoleate	Rabbit/ New Zealand White	n=6	White powder (no vehicle)	0.1 g test substance instilled into conjunctival sac of left eye (right eye used as control) using GLP in accordance with OECD TG 405; eyes (unrinsed) examined at 1, 24, 48, and 72 h post-application	Non-irritating; slight-to-moderate conjunctival irritation observed in all animals 1 and 24 h post-application, but reversed in all animals by 48 h; iris and cornea unaffected by treatment	[15]
Zinc Sulfate	Rabbit/ New Zealand White	n=3 males	Unchanged (no vehicle)	~ 98.1 mg test substance instilled into conjunctival sac of eye (untreated eye used as control) in accordance with OECD TG 405; eyes (unrinsed) observed 1, 24, 48, and 72 h and 7, 14, and 21 days post-treatment	Severely irritating; corneal injury in 2 rabbits reversed by 24 to 72 h; conjunctival irritation (redness), chemosis and discharge seen in all animals; lower eyelid tissue, nictitating membrane, and/or sclera showed yellow/white spots from day 7 through study termination; study authors considered spots (containing unknown encapsulated material causing protrusions) to be indicative of necrosis; 1 animal showed reduced eyelid elasticity at 72 h and 7 days post-treatment	[19,20]

GLP = Good Laboratory Practice; OECD TG = Organization for Economic Co-operation and Development Test Guideline

Table 16. Clinical Studies

Test Substances(s)	Test Population	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
HUMAN					
Oral					
Zinc Acetate	n=179 pregnant women in treatment group; n=345 pregnant women in control group	20 mg Zinc Aspartate	Test substance administered daily on average beginning week 25 of gestation; study was blind, randomized; controls did not receive treatment	Less pregnancy and labor maternal and fetal complications observed in treated subjects compared to controls; occurrence of large-for-date and small-for-date infants reduced in treated subjects compared to controls; no treatment-related adverse effects reported; study authors report zinc is transferred from mother to fetus through placenta	[107]
Zinc Citrate	n=13 pregnant women in treatment group; n= 16 pregnant women in control group; treatment and control patients above were compliant	100 mg Zinc Citrate equivalent to 22.5 mg zinc	Test substance or placebo administered daily during last 15 to 25 weeks of gestation; when iron/folate supplements prescribed by patient's doctor they were taken 12 h apart from test substance or placebo; criteria for trial (treatment group): subjects who smoked and this was first time pregnancy or previous small for gestational age baby; criteria for trial (control group): subjects who smoked and this was first time pregnancy or previous small for gestational age baby; low pregnancy weight	Induction of labor and intrauterine growth retardation statistically significantly lower in treatment group compared to controls; Caesarean section, placental weight, birthweight, and Ponderal index (ratio of height to weight) in treatment group not statistically different from controls; mean hemoglobin levels similar between groups; side effects attributed by patients to be from treatment included nausea and heartburn; side effects from placebo tablet reported to be aftertaste, diarrhea, lethargy, and nausea	[108]
Zinc Sulfate	n=179 pregnant women between 16 and 20 week gestation completed study (n=89 treatment group; n=90 placebo group); 196 recruited, but 6 refused participation and 11subjects excluded due to < 70% compliance during study	50 mg elemental zinc supplied as Zinc Sulfate	Randomized, double-blind study conducted; women received either test substance or placebo daily (mid-morning); 1 mg folic acid and 30 mg ferrous sulfate were also administered (at night); 20 weeks duration of supplementation in treatment and placebo groups	Average birth weight higher in treated group (3513 ± 400 g) compared to placebo (3352 ± 544) group; treatment showed no effect on neonatal head circumference and length, gestational age, or maternal complications; 2 placebo group subjects (2.2%) had infants born with intrauterine growth retardation (birth weight < 10^{th} percentile), but this did not occur in treatment group; placebo group only had 2.2% subjects with pregnancy-induced hypertension; 2 subjects in each group had stillborn fetuses or an infant death soon after birth; preterm deliveries occurred in treatment (9 subjects) and in placebo (7 subjects) groups; premature infants in treatment group were > 2500 g except 1 infant who died at 28 weeks gestation; no low birth weight occurred in treatment group, but 6 infants born in placebo group had low birth weights	[109]
Zinc Sulfate	n=246 in treatment group and 248 in control group (500 recruited but 4 moved away from area and 2 miscarried at beginning of study)	20 mg elemental zinc supplied as Zinc Sulfate	Randomized, double-blind controlled study; women received either test substance or placebo daily (after breakfast) beginning at less than 20 weeks gestation and continuing until delivery; if serum ferritin was < 10 µg/l or if hemoglobin was < 100 g/l, iron and folate supplementation administered (in the evening); for a 7 day period daily food diaries kept (gestation weeks 28-32) for comparison	Pregnancy complications and labor and delivery no different in treatment group compared to controls; no lower occurrence of growth retardation or neonatal abnormalities in treatment compared to control group; no statistically significant difference in daily food/nutrient intakes in treatment compared to control groups (mean intake of dietary zinc ~9 mg, about half of recommended 20 mg/day intake for pregnant women); study researchers reported no detectable difference of subjects treated with zinc supplementation during pregnancy compared to controls	[110]

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