

Safety Assessment of Zinc Salts as Used in Cosmetics

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Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 27 inorganic and organometallic zinc salts as used in cosmetic formulations; these salts are specifically of the 2^+ (II) oxidation state cation of zinc. These ingredients included in this report have various reported 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 Panel reviewed the relevant data for these ingredients, and concluded that these 27 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

Keywords

Cosmetics, Safety, 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 Undecylenate

Introduction

This assessment reviews the safety of the following 27 inorganic and organometallic zinc salts as used in cosmetic formulations:

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

The following zinc salts have been reviewed previously by the Panel and determined to be safe for use in cosmetic products according to the use concentrations and practices specified in their respective safety assessments: Zinc Acetate

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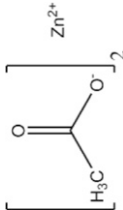
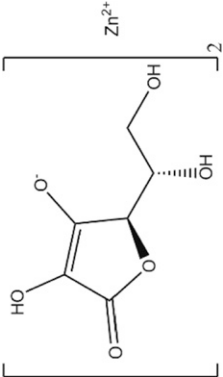
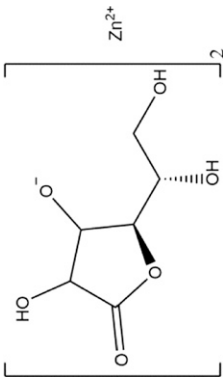
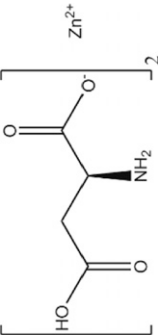
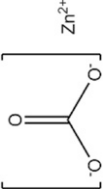
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Table 1. Definitions, Structures, and Functions of the Ingredients in This Safety Assessment (¹. CIR Staff)

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

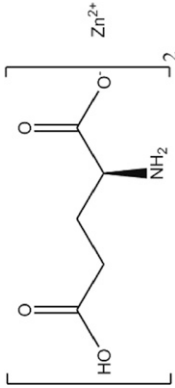
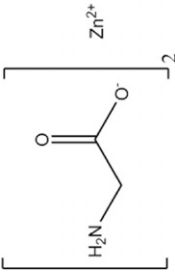
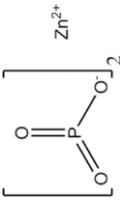
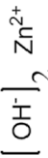
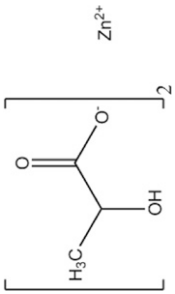
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Table 1. (continued)

Ingredient CAS No.	Definition & Structure		Function
Zinc Carbonate Hydroxide	Zinc Carbonate Hydroxide is an inorganic basic carbonate that conforms generally to the formula:		bulking agents; pH adjusters
	$4 \left(\left[\begin{array}{c} \text{O} \\ \parallel \\ \text{O} - \text{C} - \text{O}^- \\ \\ \text{O}^- \end{array} \right] \text{Zn}^{2+} \right) 2 \left(\left[\text{OH}^- \right]_2 \text{Zn}^{2+} \right) \cdot 5 \text{H}_2\text{O}$		
Zinc Chloride 7646-85-7	According to this formula, this ingredient is the pentahydrate. Zinc Chloride is the inorganic salt that conforms to the formula: $[\text{Cl}^-]_2 \text{Zn}^{2+}$		cosmetic astringents; cosmetic biocides; drug astringents-oral health care drugs; oral care agents; oral health care drugs bulking agents
Zinc Chloride Hydroxide 12167-79-2	Zinc Chloride Hydroxide is the inorganic compound that conforms to the formula: $\text{Zn}_5(\text{OH})_8\text{Cl}_2 \cdot \text{H}_2\text{O}$		
Zinc Citrate 546-46-3	According to this formula, this ingredient is the monohydrate. Zinc Citrate is the zinc salt of citric acid that conforms to the formula: $\left[\begin{array}{c} \text{O}^- \\ \parallel \\ \text{O} - \text{C} - \text{CH}(\text{OH}) - \text{CH}_2 - \text{COO}^- \\ \\ \text{O}^- \end{array} \right]_2 \cdot 3 \text{Zn}^{2+}$		cosmetic biocides; oral care agents
Zinc Cysteinate 1197186-61-0	Zinc Cysteinate is the organic salt that conforms to the formula: $\left[\begin{array}{c} \text{O} \\ \parallel \\ \text{O} - \text{C} - \text{CH}(\text{NH}_2) - \text{CH}_2 - \text{SH} \end{array} \right]_2 \text{Zn}^{2+}$		cosmetic biocides
Zinc Gluconate 4468-02-4	Zinc Gluconate is the zinc salt of gluconic acid that conforms to the formula: $\left[\begin{array}{c} \text{HO} \\ \\ \text{CH}_2 - \text{CH}(\text{OH}) - \text{CH}(\text{OH}) - \text{CH}(\text{OH}) - \text{CH}(\text{OH}) - \text{COO}^- \end{array} \right]_2 \text{Zn}^{2+}$		cosmetic biocides; skin-conditioning agents-miscellaneous

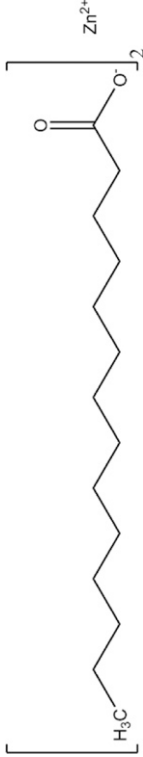
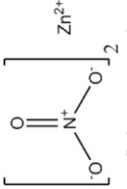
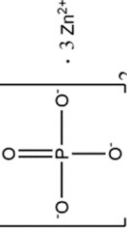
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Table 1. (continued)

Ingredient CAS No.	Definition & Structure	Function
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; oral care agent
Zinc Laurate 2452-01-9	Zinc Laurate is the salt of lauric acid that conforms generally to the formula: 	antickling agents; slip modifiers; viscosity increasing agents-non-aqueous

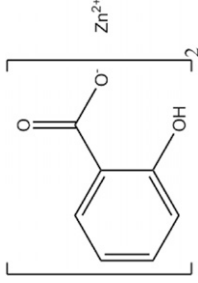
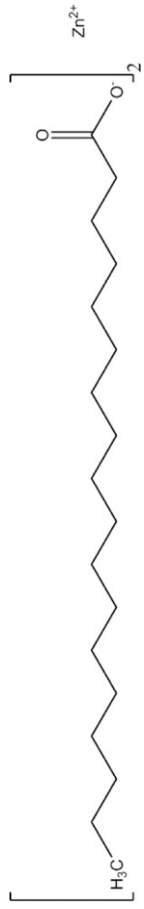
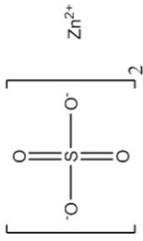
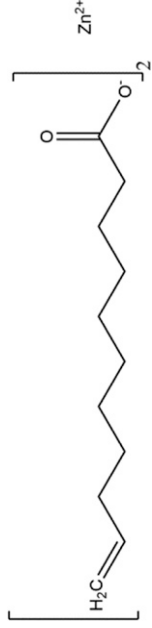
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Table 1. (continued)

Ingredient CAS No.	Definition & Structure		Function
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
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

(continued)

Table 1. (continued)

Ingredient CAS No.	Definition & Structure	Function
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 Undecylenate 557-08-4	Zinc Undecylenate is the salt of undecylenic acid that conforms generally to the formula: 	anticaking agents; antifungal agents; cosmetic biocides

(2012),² Zinc Citrate (2014),³ Zinc Myristate (2010),⁴ Zinc Ricinoleate (2007),⁵ and Zinc Stearate (1982; reaffirmed in 2002).^{6,7} For complete and detailed information, please refer to the original documents, which are available on the Cosmetic Ingredient Review (CIR) website (<https://www.cir-safety.org/ingredients>).

Some of the constituent acids or salts, related to the zinc salt ingredients in this report, have been reviewed previously by the Panel; a summary of safety conclusions for those ingredients^{2-5,8-18} 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 local effects (e.g., dermal exposure, irritation and sensitization), rather than oral toxicity and bioavailability.

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 the Panel typically evaluates, is provided on the CIR website (<https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <https://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Some of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.¹⁹⁻³³ 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)³⁴⁻³⁶ and the United States (US) Food and Drug Administration (FDA).³⁷⁻⁴⁷

Chemistry

Definition and Structure

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

An example structure of Zinc Citrate is provided below (Figure 1B).

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 101.41 g/mol (Zinc Hydroxide) to 660 g/mol (Zinc Ricinoleate). 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 is insoluble in water, alcohol, and ether and is soluble in benzene.

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)⁴⁸ of Zinc Chloride Hydroxide in 3 batches tested was <0.025 g/m³ (or <0.016 g/m³ as free zinc).⁴⁹ 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). The “total dustiness” (i.e., airborne fraction) of Zinc Laurate is 241.82 mg/g (34 mg/g of free zinc).³³ The mass median aerodynamic diameter (MMAD) of total dustiness (monomodal distribution) is 8.50 µm (distribution fitted to cascade impactor data); the geometric standard deviation (GSD) of MMAD is 4.36.

Method of Manufacture

Methods of manufacture of zinc salts are described in Table 4.⁴⁹⁻⁵⁸

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.⁵⁹ The acceptance criteria are no less than (NLT) 98% and no more than (NMT) 102%.

Zinc Carbonate. Cadmium is a “minor constituent” of smithsonite,⁵¹ which is a mineral consisting chiefly of zinc carbonate.¹

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 (e.g., zinc oxide) and oxidation with sodium hypochlorite (i.e., bleach) or chlorine.⁵²

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.⁵⁹ The acceptance criteria are NLT 97% and NMT 102%.

Table 2. Conclusions and Dermal Irritation and Sensitization Data and Ocular Irritation Data for Constituent Acids (Counter Anions to Zinc) and Related Salts Previously Reviewed by the Panel (e.g., Acetic Acid for Zinc Acetate).

Ingredient	Conclusion (year issued)* and dermal and ocular data	Reference
CONSTITUENT ACIDS		
Acetic Acid	Safe in the present practices of use and concentration (2012) <u>Irritation/sensitization:</u> glacial acetic acid (equivalent to 95% Acetic Acid) caused complete destruction of the skin of guinea pigs after 24 h; 28% Acetic Acid only produced moderate irritation in 24 h; after 4-h exposure to 10% Acetic Acid, 70-94% of volunteers reported dermal irritation <u>Ocular:</u> >10% Acetic Acid caused severe of permanent eye injury in rabbits; a 5% solution caused severe but reversible damage	2
L-Ascorbic Acid	Safe as used (2005) <u>Irritation/sensitization:</u> a product containing 10% Ascorbic Acid was a non-irritant in a 4-day mini-cumulative patch assay; an opaque cream containing 5% Ascorbic Acid did not induce dermal sensitization in 103 human subjects; a facial treatment containing 10% Ascorbic Acid was not a contact sensitizer in a maximization assay with 26 subjects <u>Ocular:</u> no data reported	8
Aspartic Acid	Safe in the present practices of use and concentration (2013) <u>Irritation/sensitization:</u> in an EpiSkin assay, an eye gel containing 0.2% aspartic acid was potentially a non-irritant; an eye gel containing 0.2% and a hair masque containing 0.92% aspartic acid were not irritants or sensitizers in in HRIPTs <u>Ocular:</u> an eye gel containing 0.2% aspartic acid was weakly irritating in a BCOP assay and moderately irritating in a HET-CAM assay	9
Citric Acid	safe in the present practices of use and concentration (2014) <u>Irritation/sensitization:</u> in irritation studies in rabbits, 30% Citric Acid was not a primary irritant, 60% produced some erythema and edema that subsided with time, and undiluted Citric Acid produced mild to severe erythema and mild to moderate edema; in human studies, Citric Acid was not a dermal irritant at concentrations up to 5% aq; Sodium Citrate did not produce any immediate (non-immunologic contact urticaria) reactions; in sensitization testing, a cuticle cream containing 4% Citric Acid was not an irritant or a sensitizer in humans; 2.5% aq. Citric Acid produced positive results in skin prick test in 3 of 91 urticaria or angioedema patients <u>Ocular:</u> Citric Acid was predicted to be a moderate/severe to severe/extreme ocular irritant in in vitro studies, and it was minimally irritating to rabbit eyes at a concentration of 10% and mildly irritating at a concentration of 30%	3
Gluconic Acid	Safe in the present practices of use and concentration (2014) <u>Irritation/sensitization:</u> a 50% aq. solution of Gluconic Acid was not a dermal irritant in rabbits <u>Ocular:</u> Gluconic Acid, as a 50% aq. solution, was not irritating to rabbit eyes	10
Glutamic Acid	Safe in the present practices of use and concentration (2013) <u>Irritation/Sensitization:</u> negative in cell-based in vitro gene expression studies to identify skin sensitizers; 0.01% in a face and neck product was not an irritant or sensitizer in a HRIPT <u>Ocular:</u> no data reported	

(continued)

Table 2. (continued)

Ingredient	Conclusion (year issued)* and dermal and ocular data	Reference
Lactic Acid	Safe for use at concentrations $\leq 10\%$, 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 $\leq 30\%$, 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 <u>Irritation/Sensitization:</u> mini-cumulative irritation patch assays were performed with creams and lotions containing 4–8% Lactic Acid at a pH range of 3.8–5.0; skin irritation ranged from essentially nonirritating to moderately irritating; no correlation between pH and/or concentration was observed. In facial discomfort assays with creams and lotions containing 4–10% Lactic Acid, pH 3.3–4.3, discomfort ranged from nonstinging to moderate stinging; no correlation between pH and/or concentration was observed. <u>Ocular:</u> in vitro, face, eye and nail formulations containing 0.12–11.8% of 85% aq. Lactic Acid, pH 2.0–7.5, were minimal to moderate-severe ocular irritants, skin and hair products containing 0.15–20% of 60% aq. Sodium Lactate, pH 3.2–3.8 were minimal irritants; in in vivo testing for ocular irritation with Lactic Acid, a skin cream containing 0.6% of 85% aq. Lactic Acid, pH 7.5, caused minimal irritation and a solution containing below-20% Lactic Acid, pH not given, produced significant irritation; 60% aq. Potassium Lactate, pH 8.1, was slightly irritating, and 50–70% Sodium Lactate caused no significant ocular irritation; face and hair products containing 0.1–0.4% of 60% aq. Sodium Lactate, pH 3.4–8.6, caused no to mild ocular irritation and a 100% solution produced irritation	11
Lauric Acid	Safe in the present practices of use and concentration (1987); reaffirmed 2006 <u>Irritation/sensitization:</u> in a HRIPT, 1% Lauric Acid in formulation was not an irritating or sensitizer <u>Ocular:</u> in rabbits, a 1% aq dilution of a soap formulation containing 1.5% Lauric Acid and a 8% aq dilution of a formulation containing 8.7% Lauric Acid were not irritants; commercially supplied Lauric Acid produced persistent corneal opacity, mild conjunctivitis, iritis	12,13
Myristic Acid	Safe in the present practices of use and concentration (2010) <u>Irritation/sensitization:</u> in human subjects, a cleanser formulation containing 5% Myristic Acid was highly irritating in a 21-day cumulative irritation study, bar soap formulations containing 8% were slightly to moderately irritating in the soap chamber test; 50% in mineral oil was non-irritating in the soap chamber test; Myristic Acid as commercially supplied was practically non-irritating in a SIOPT <u>Ocular:</u> in rabbits, formulations containing 1.5–50% Myristic Acid, and Myristic Acid as commercially supplied, were not irritants	4,12,13

(continued)

Table 2. (continued)

Ingredient	Conclusion (year issued)* and dermal and ocular data	Reference
Palmitic Acid	Safe in the present practices of use and concentration (1987); reaffirmed 2006 <u>Irritation/sensitization:</u> a formulation containing 2.2% Palmitic Acid was not irritating to human skin with single open and occlusive patches, and it was not irritating or sensitizing in a HRIPT <u>Ocular:</u> in rabbits, formulations containing 2.2–19.4% Palmitic Acid, and Palmitic Acid as commercially supplied, were not irritants	12,13
Ricinoleic Acid	Safe in the present practices of use and concentration (2007) <u>Irritation/sensitization:</u> Neither erythema nor edema was observed following a single topical application of Ricinoleic Acid (in peanut oil) to the paws of 8 to 10 male Swiss mice; application of Ricinoleic Acid (in peanut oil) to the entire eyelid surface of each of six male albino Dunkin-Hartley guinea pigs induced eyelid reddening and edema at doses of 10, 30, or 100 mg. <u>Ocular:</u> no data reported	5
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) <u>Irritation/sensitization:</u> in LLNAs, 20% Salicylic Acid in acetone was positive, but 20% in acetone/olive oil was not; in clinical cumulative irritation studies, 1.5% Salicylic Acid produced slight or no irritation and 2% had minimal cumulative irritation; not a sensitizer in normal skin <u>Ocular:</u> no data reported	14
Stearic Acid	Safe in the present practices of use and concentration (1987); reaffirmed 2006 <u>Irritation/Sensitization:</u> in 13-week dermal toxicity studies, 2 cosmetic product formulations containing, at most 5% Stearic Acid produced moderate skin irritation in rats receiving 4.0 ml/kg and 227 mg/kg doses.; in human studies, 8% (in formulation) up to 40% (in mineral oil) was non-irritating. In SIOPTs; ; formulations containing 2.6 and 2.8% were basically non-irritating and moderately irritating, respectively, in 21-day cumulative irritation tests; 13% in formulation was non-irritating in a 4-wk use test; Stearic Acid was not a sensitizer in humans when tested at concentrations ranging from 0.5% to 13% <u>Ocular:</u> in rabbits, formulations containing 1–65% Stearic Acid, and Stearic Acid as commercially supplied, was at most slightly irritating	12,13
SALTS		
Carbonate Salts	Safe when formulated to be non-irritating (2017)	15
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)	16
Sodium Hexametaphosphate and Phosphate Salts	Safe when formulated to be non-irritating (2016)	17
Sodium Sulfate	Safe when formulated to be non-irritating (2016)	18

Abbreviations: BCOP, bovine cornea opacity permeability test; HET-CAM, hen's egg test – chorioallantoic membrane test; HRIPT, human repeated insult patch test; LLNA, local lymph node assay; SIOPT, single insult occlusive patch test.

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

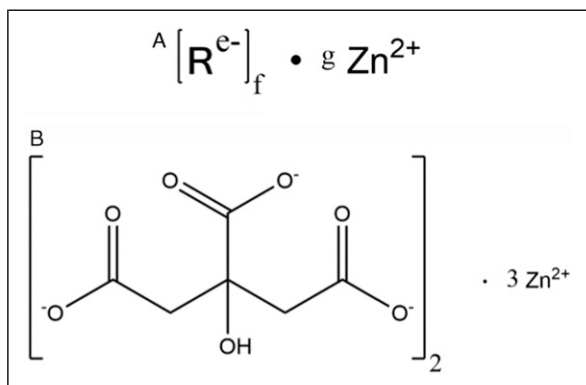


Figure 1. (A) Zinc salts, wherein R is an anion and $e \cdot f = g \cdot 2$. (B) Zinc Citrate, an example salt (wherein R is citrate, e is 3 (1 for each "O⁻"), f is 2, and g is 3).

Zinc Stearate. According to the *FCC*, food grade specifications limit impurities in Zinc Stearate as follows: ≤ 10 mg (1.0%) residue weight of alkalis and alkaline earth metals, ≤ 1.5 mg/kg arsenic, ≤ 250 mg/kg chloride, ≤ 2 mg/kg lead, and $\leq 0.6\%$ sulfate.⁵⁹ The acceptance criteria are NLT 10% and NMT 12% of zinc. Zinc Stearate is typically a mixture of Zinc Stearate and Zinc Palmitate and may contain zinc oxide (13.5% to 15%).⁵⁴

Zinc Sulfate. According to the *FCC*, food grade specifications limit impurities in Zinc Sulfate as follows: ≤ 5 mg (0.5%) residue weight of alkalis and alkaline earth metals, ≤ 2 mg/kg cadmium, ≤ 4 mg/kg lead, ≤ 5 mg/kg mercury, and $\leq 0.003\%$ selenium.⁵⁹ The acceptance criteria are NLT 98% and NMT 100.5% for monohydrate and NLT 99% and NMT 108.7% for heptahydrate.

Natural Occurrence

Generally, zinc salts are found in some seafood, red meats, and whole grains.⁶⁰ Human tissues and body fluids contain zinc salts. Human blood has been reported to contain zinc salt concentrations of 0.7 to 1.8 $\mu\text{g/mL}$.⁶¹ In humans, most of the zinc is found in muscle and bones ($\sim 85\%$); total body zinc in men and women is approximately 2.5 and 1.5 g, respectively.⁶² Smaller amounts of zinc are located in the skin and hair ($\sim 8\%$), liver ($\sim 5\%$), and gastrointestinal tract and pancreas ($\sim 3\%$).^{36,63}

Zinc Carbonate. The naturally occurring minerals smithsonite and zincspar contain Zinc Carbonate.⁵⁴

Zinc Carbonate Hydroxide. Zinc Carbonate Hydroxide occurs naturally as the mineral hydrozincite.⁵⁴

Zinc Phosphate. Zinc Phosphate occurs naturally as the mineral hopeite.⁵⁴

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 US 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 2017⁶⁴ and Council survey data collected in 2016 and 2017⁶⁵ indicate that 18 ingredients included in this safety assessment are used in cosmetic formulations.

According to 2017 VCRP data, Zinc Stearate and Zinc Gluconate have the highest number of reported uses at 2321 and 318 uses, respectively (Table 5).⁶⁴ 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).⁶⁴ 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).^{66,67}

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^{64,66}; 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 are indicated in *italics* (Table 5).

Several of the zinc salts are used in cosmetics that are oral care products; for example, dentifrices are reported to contain up to 2% Zinc Citrate or Zinc Stearate.⁶⁵ Use in these types of products can result in incidental ingestion or in a retained fraction after use. Several of the ingredients are also used in lipsticks; for example, Zinc Myristate is used at up to 5% in lipstick formulations. Although lipsticks are applied to the mucous membrane surface of the lips, dermal exposure is possible in the perioral area, and incidental ingestion may occur with this product type as well. Because it is possible for the incidental ingestion of zinc through the use of these products, the concentration of zinc present via a zinc salt (determined using zinc molecular and formula weights) that is used in oral

Table 3. Physical and Chemical Properties.

Property	Value	Reference
Zinc Acetate		
Physical Form	Crystalline solid	151
Color	White	151
Formula Weight (g/mol)	183.5 (anhydrous); 219.53 (dihydrate)	54
Density (g/mL) @ 20°C	1.74	151
Melting Point (°C)	237	152
Water Solubility (g/L)	435 (dihydrate)	54
Other Solubility (g/L)	33 in alcohol (dihydrate)	54
Log P	-1.28 (est.)	153
Zinc Ascorbate		
Formula Weight (g/mol)	415.612 (est.)	154
Log P	-1.85 (est.)	153
Zinc Ascorbate Hydroxide		
Formula Weight (g/mol)	483.64 (est.)	155
Log P	0.42 (est.)	153
Zinc Aspartate		
Formula Weight (g/mol)	329.57 (est.)	156
Log P	-3.89 (est.)	153
Zinc Carbonate		
Physical Form	Crystalline solid	157
Color	White	157
Formula Weight (g/mol)	125.42	54
Density (g/mL) @ 20°C	4.4	158
Water Solubility (g/L) @ 15°C	0.01	54
Other Solubility	Soluble in dilute acids, alkalis, and ammonium salt solutions	54
Log P	-2.02 (est.)	153
Zinc Carbonate Hydroxide		
Formula Weight (g/mol)	143.403 (est.)	159
Zinc Chloride		
Physical Form	Granules	54
Color	White	54
Formula Weight (g/mol)	136.31	54
Density (g/mL) @ 25 °C	2.907	54
Melting Point (°C)	327.9	54
Boiling Point (°C)	732	54
Water Solubility (g/L) @ 25°C	4320	54
Other Solubility	Soluble in 2% HCl _(aq) , alcohol, glycerol, acetone	54
Zinc Chloride Hydroxide		
Physical Form	powder	160
Color	white to off-white	160
Formula Weight (g/mol)	551.88	160
Density (g/mL)	3.1–3.3	160
Water Solubility	insoluble	160
Zinc Citrate		
Formula Weight (g/mol)	574.43	54
Water Solubility	Slightly soluble in water (dihydrate)	54
Other Solubility	Soluble in dilute mineral acids and in alkali hydroxides (dihydrate)	54
Log P	-2.09 (est.)	153
Zinc Cysteinate		
Formula Weight (g/mol)	185.5446	161
Log P	-7.50 (est.)	153

(continued)

Table 3. (continued)

Property	Value	Reference
Zinc Gluconate		
Physical Form	Granular or crystalline powder	59
Color	White	59
Formula Weight (g/mol)	455.68	59
Melting Point (°C)	172-175	162
Water Solubility	Freely soluble	59
Other Solubility	Very slightly soluble in alcohol	59
Log P	-7.41 (est.)	153
Zinc Glutamate		
Formula Weight (g/mol)	210.494 (est.)	163
Log P	-2.04 (est.)	153
Zinc Glycinate		
Formula Weight (g/mol)	213.498 (est.)	164
Melting Point (°C)	> 300	165
Log P	-3.21 (est.)	153
Zinc Hexametaphosphate		
Formula Weight (g/mol)	223.322 (est.)	166
Log P	-1.72 (est.)	153
Zinc Hydroxide		
Formula Weight (g/mol)	101.41 (est.)	167
Density (g/mL)	3.053	36
Melting Point (°C)	125	36
Water Solubility	Very slightly soluble	36
Other Solubility	Soluble in acid and alkali	36
Log P	-0.77 (est.)	153
Zinc Lactate		
Physical Form	Crystals (trihydrate)	54
Formula Weight (g/mol)	243.52	168
Water Solubility	Soluble (trihydrate)	54
Log P	-2.97 (est.)	153
Zinc Laurate		
Physical Form	Odorless powder	33
color	white	33
Formula Weight (g/mol)	464.008 (est.)	168
Density (g/mL)	1.09	169
Melting Point (°C)	130-135	169
Dustiness (airborne fraction)	241.82 mg/g	33
	MMAD of total dustiness: 8.50 µm; GSD of MMAD: 4.36	
Log P	8.54 (est.)	153
Zinc Myristate		
Formula Weight (g/mol)	520.116	170
Density (g/mL) @ 20 °C and 760 mmHg	1.16	171
Melting Point (°C)	130-134	171
Log P	10.51 (est.)	153
Zinc Neodecanoate		
Formula Weight (g/mol)	409.916 (est.)	172
Log P	6.14 (est.)	153
Zinc Nitrate		
Physical Form	Powder	55
Color	White	55
Formula Weight (g/mol)	189.42	54

(continued)

Table 3. (continued)

Property	Value	Reference
Density (g/mL)	2.065 (hexahydrate)	54
Melting Point (°C)	~36 (hexahydrate)	54
Water Solubility	Soluble in water (hexahydrate)	54
Other Solubility	Freely soluble in alcohol (hexahydrate)	54
Log P	-0.51 (est.)	153
Zinc Palmitate		
Formula Weight (g/mol)	576.224	173
Density (g/mL)	1.14	174
Melting Point (°C)	129–135	174
Log P	12.47 (est.)	153
Zinc Phosphate		
Physical Form	Powder	54
Color	White	54
Formula Weight (g/mol)	386.17	54
Density (g/mL)	3.16 (experimental)	175
Water Solubility	Insoluble	54
Other Solubility	Insoluble in alcohol; soluble in dilute mineral acids, acetic acid, ammonia, and alkali hydroxide solutions	54
Log P	-0.77 (est.)	153
Zinc Ricinoleate		
Formula Weight (g/mol)	660.298 (est.)	176
Log P	11.34 (est.)	153
Zinc Salicylate		
Physical Form	Crystal powder or needles	54
Formula Weight (g/mol)	339.64	54
Water Solubility	Soluble	54
Other Solubility	Soluble in alcohol	54
Log P	3.18 (est.)	153
Zinc Stearate		
Physical Form	Powder	59
Color	White	59
Formula Weight (g/mol)	632.3	59
Density (g/mL)	1.1	177
Melting Point (°C)	120	54
Water Solubility	Practically insoluble	59
Other Solubility	Insoluble in alcohol and ether; soluble in benzene	54
Log P	14.44 (est.)	153
Zinc Sulfate		
Physical Form	Transparent prisms, small needles, or granular crystalline powder	59
Color	Colorless	59
Formula Weight (g/mol)	179.45 (monohydrate); 287.54 (heptahydrate)	59
Density (g/mL)	1.97 (heptahydrate)	54
Melting Point (°C)	100 (heptahydrate)	54
Water Solubility	Soluble (mono- and heptahydrate)	59
Other Solubility	Insoluble in alcohol (mono- and heptahydrate); soluble in glycerine (heptahydrate)	59
Log P	-0.07 (est.)	153
Zinc Undecylenate		
Formula Weight (g/mol)	431.922 (est.)	178
Melting Point (°C)	115–116	179
Log P	7.29 (est.)	153

Abbreviation: GSD, geometric standard deviation; MMAD, mass median aerodynamic diameter.

Table 4. Methods of Manufacture.

Ingredient	Method
Zinc Acetate	prepared by reacting zinc oxide with acetic acid ⁵⁰
Zinc Carbonate	prepared via grinding the mineral smithsonite ⁵¹
Zinc Chloride	can be made by reacting aqueous hydrochloric acid and zinc scrap materials or roasted ore ⁵² 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 ⁵³ 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 diamine chloride (5% to 9%); zinc diamine chloride is partially removed by water in subsequent steps while the remaining portion undergoes conversion to zinc oxide (<9%) ⁴⁹
Zinc Citrate	formed from Zinc Carbonate and citric acid ⁵⁴
Zinc Lactate	prepared from lactic acid and Zinc Carbonate ⁵⁴
Zinc Nitrate	can be prepared by reacting nitric acid with zinc or zinc oxide ⁵⁵
Zinc Salicylate	prepared from Zinc Sulfate and sodium salicylate ⁵⁴
Zinc Stearate	prepared from Zinc Chloride and stearic acid ⁵⁴ can also be prepared by reacting sodium stearate with a Zinc Sulfate solution ⁵⁶
Zinc Sulfate	can be prepared by combining dilute sulfuric acid with zinc hydroxide, followed by crystallization of the supernatant with acetone ⁵⁸ reaction of sulfuric acid and zinc oxide ⁵⁷
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 ⁵⁸

care products or lipsticks is also included in Table 5. The greatest reported concentration of zinc present in oral care products and in lipstick formulations is 0.22% via Zinc Citrate (in a dentifrice) and 0.61% via Zinc Myristate, respectively.

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%)⁶⁶ and Zinc Stearate is reportedly used in baby lotions, oils, powders, and creams.⁶⁴

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%. 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.⁶⁸⁻⁷¹ 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.^{69,70} 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.⁷⁰ 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% and 20% and could possibly be inhaled. The VCRP indicates that Zinc Laurate is reportedly used in face powders.⁶⁴ 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.⁷²⁻⁷⁴

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 water-soluble zinc salts (Zinc Acetate, Zinc Chloride, Zinc Gluconate, and Zinc Glutamate) with the exception of zinc 4-hydroxybenzenesulphonate (entry 25) and zinc pyrithione (entry 101 and Annex V, entry 8) to a maximum of 1%.⁷⁵ According to Annex IV/150, Zinc Stearate is included on the “list of colorants allowed in cosmetic products.”⁷⁶

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.^{77,78} 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. Therefore, BfR proposed that the maximum zinc concentration in mouthwashes for adults not exceed 0.1% and that these products should not contain free zinc for people under the age of 18.

Table 5. Frequency and Concentration of Use According to Duration and Type of Exposure for Zinc Salts.^{2-5,7,64,65}

	# 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	not oral: 0.05
Baby Products	NR	NR	NR	NR	NR	0.01
	Zinc Aspartate		Zinc Carbonate		Zinc Chloride	
	2017	2016	2017	2016	2017	2016
Totals*	25	NR	1	1.6	70	0.000095–0.47
Duration of Use						
Leave-On	8	NR	11	NR	61	0.0001–0.47
Rinse-Off	17	NR	NR	1.6	9	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	5	oral care: 0.088 (0.041% Zn)
Incidental Inhalation-Spray	spray: NR possible: 5 ^a , 2 ^b	NR	spray: NR possible: 1 ^b	NR	spray: 1 possible: 11 ^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	1	NR	62	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

(continued)

Table 5. (continued)

Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	I	NR	NR	NR	5	oral care: 0.088 (0.041% Zn)
Baby Products	NR	NR	NR	NR	NR	NR
	Zinc Citrate**		Zinc Citrate		Zinc Gluconate	
	2011	2011	2017	2016		
Totals*	9	0.05–2	12	0.05–2	321	0.000005–3
Duration of Use						
Leave-On	5	0.05	6	NR	255	0.00024–3
Rinse-Off	4	0.3–2	6	0.05–2	66	0.00005–0.5
Diluted for (Bath) Use	NR	NR	NR	NR	NR	0.000005
Exposure Type						
Eye Area	NR	NR	NR	NR	35	0.0048–3
Incidental Ingestion	4	0.3–2	5	oral care: 0.28–2 (0.031–0.22% Zn)	9	lipstick: 0.1 (0.031% Zn)
Incidental Inhalation-Spray	NR	NR	possible: 2 ^a	spray: NR possible: 0.28 ^a	spray: NR possible: 81 ^a , 71 ^b	spray: NR possible: 0.001 ^a
Incidental Inhalation-Powder	NR	powder: 0.05	NR	NR	powder: I possible: 71 ^b	powder: NR possible: 0.001–1 ^c
Dermal Contact	5	0.05	6	0.05	286	0.000005–3
Deodorant (underarm)	4 ^a	NR	2 ^a	NR	14 ^a	NR
Hair - Non-Coloring	NR	NR	I	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	6	oral care: 0.28–2 (0.031–0.22% Zn) not oral: 0.05	17	lipstick: 0.1 (0.031% Zn) not oral: 0.000005
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	NR	0.25–1.8
Duration of Use						
Leave-On	NR	0.009	2	NR	NR	NR
Rinse-Off	NR	NR	NR	NR	NR	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	NR	oral care: 0.25–0.44 (0.065–0.12% Zn)
Incidental Inhalation-Spray	NR	NR	spray: NR possible: 1 ^a , 1 ^b	NR	NR	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

(continued)

Table 5. (continued)

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	NR	oral care: 0.25–0.44 (0.065–0.12% Zn)
Baby Products	NR	NR	NR	NR	NR	NR
	Zinc Laurate		Zinc Myristate**		Zinc Myristate	
	2017	2016	2007	2006	2017	2016
Totals*	60	1–7	122	0.00005–20	33	0.005–20
Duration of Use						
Leave-On	45	1–7	122	0.00005–20	33	0.005–20
Rinse-Off	15	1.2	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	6	NR	60	0.05–6	14	0.51–20
Incidental Ingestion	NR	NR	NR	5	NR	lipstick: 0.063–5 (0.0077–0.61% Zn)
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: 20 possible: 5 ^b	powder: 14 possible: NR	powder: 2–20 possible: 5–15 ^c
Dermal Contact	50	1–7	117	0.001–20	33	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	3	NR	NR	5	NR	lipstick: 0.063–5 (0.0077–0.61% Zn)
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	21	0.15–2.3
Duration of Use						
Leave-On	NR	NR	2	1–2	20	0.15–2.3
Rinse-Off	NR	1	1	NR	1	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	oral care: 1 (0.17% Zn)	NR	NR	2	lipstick: 1.1 (0.11% Zn)
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	17	0.15–2.3
Deodorant (underarm)	NR	NR	2 ^a	2 ^a	16 ^a	spray: 0.82–2.3 not spray: 0.82–2
Hair - Non-Coloring	NR	NR	NR	1	1	NR

(continued)

Table 5. (continued)

Hair-Coloring	NR		NR	NR	NR	NR	NR
Nail	NR		NR	NR	NR	1	NR
Mucous Membrane	NR	oral care: 1 (0.17% Zn)		NR	NR	2	lipstick: 1.1 (0.11% Zn)
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	2204	0.2–32
Duration of Use							
Leave-On	NR	0.47	742	0.5–51	2198		0.2–32
Rinse-Off	NR	NR	2	1	6		0.28–3.3
Diluted for (Bath) Use	NR	NR	2	3	NR		NR
Exposure Type							
Eye Area	NR	NR	346	1–16	1369		1–32
Incidental Ingestion	NR	NR	2	3	3	oral care: 2 (0.2% Zn)	lipstick: 0.5 (0.05% Zn)
Incidental Inhalation-Spray	NR	NR	spray: NR possible: 2 ^a , 5 ^b	spray: 2 possible: 1–2 ^a , 1–2 ^b	spray: NR possible: 7 ^a , 7 ^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: 416 possible: 7 ^b , 1 ^c		powder: 1.1–14 possible: 0.2–1 ^c
Dermal Contact	NR	0.47	738	0.5–51	2193		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	3	oral care: 2 (0.2% Zn)	lipstick: 0.5 (0.05% Zn)
Baby Products	NR	NR	2	0.5	1		NR
		Zinc Sulfate***				Zinc Undecylenate	
		2017		2016		2017	2016
Totals*		149		0.0001–1		NR	0.25
Duration of Use							
Leave-On		86		0.0001–1		NR	0.25
Rinse-Off		63		0.0003–0.15		NR	NR
Diluted for (Bath) Use		NR		NR		NR	NR
Exposure Type							
Eye Area		11		0.02		NR	NR
Incidental Ingestion		1		NR		NR	NR
Incidental Inhalation-Spray		spray: NR possible: 15 ^a , 19 ^b		spray: NR possible: 0.003 ^a		NR	spray: NR possible: 0.25 ^b
Incidental Inhalation-Powder		powder: 5 possible: 19 ^b		powder: 0.02 possible: 0.0008–0.12 ^c		NR	powder: NR possible: 0.25 ^b

(continued)

Table 5. (continued)

Dermal Contact	103	0.0003–1	NR	0.25
Deodorant (underarm)	NR	0.0015	NR	NR
Hair - Non-Coloring	37	0.003–0.15	NR	NR
Hair-Coloring	NR	NR	NR	NR
Nail	8	0.0001–0.001	NR	NR
Mucous Membrane	15	not oral: 0.0003–0.057	NR	NR
Baby Products	NR	NR	NR	NR

* 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.

^aIncludes products that can be sprays, but it is not known whether the reported uses are sprays.

^bNot 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.

^cIncludes 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.^{64,66,67}

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

Cosmetics Europe conducted an aggregate exposure assessment, and in 2016 it was concluded that the combined food and oral care products exposures, including use of the allowed 1% zinc concentration in toothpastes, was safe for all age groups, and supported a maximum concentration of up to 0.1% zinc in mouthwashes for ages 6 years and older.⁷⁹

The European Commission Scientific Committee on Consumer Safety (SCCS) published an opinion on water-soluble zinc salts used in oral hygiene products.⁷⁹ 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 aged 6–17 years. This exposure constitutes up to 14% of the 25 mg/day upper limit for adults and 35% of the 10 mg/day upper limit for children aged 6 for zinc; the SCCS considered the use of zinc in toothpaste and mouthwash *per se* to be safe for adults and children aged 6–17 years. In children 0.5–5 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 constitutes up to 14–29% of the upper limit of 7 mg/day for children aged 0.5–3 years and up to 10–20% of the upper limit of 10 mg/day for children aged 4–5 years; the SCCS considers that the use of zinc in toothpaste *per se* is safe for children aged 0.5–5 years. The use of mouthwash is not recommended in children age 5 and younger. The SCCS also noted that it could not advise on the percentage of the zinc upper limit to attribute to cosmetic exposure. “The SCCS is aware that upper limits

may be exceeded in some cases because the default values used in this Opinion are based on conservative estimates.”

Non-Cosmetic

The uses of many zinc salts, as specified in Title 21 of the Code of Federal Regulations (21CFR), are indirect food additives in packaging contacting food or as direct nutritional food additives intended for animal and human consumption (Table 7). In the US, 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 daily allowances (RDAs) for zinc are 11 mg/day for men and 8 mg/day for women.⁸⁰ 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.⁸¹ 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.

Zinc Acetate (25 mg zinc) is used in an oral capsule prescription drug product approved by the FDA.³⁷ Zinc Chloride (1 mg zinc/mL equivalent) is used in an injectable prescription drug product approved by the FDA.³⁸ The World

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 -Indirect food additives; adjuvants, production aids, sanitizers; rosins and rosin derivatives; zinc salts may be used in saponification of rosins	21CFR172.325 21CFR178.3870
Zinc Salts of Fatty Acids	-Ingredient food additives, polymers, rubber articles; zinc salts of fatty acids may be used as activators ($\leq$ 5% by weight of rubber product)	21CFR177.2600
Zinc Acetate	-Indirect food additive, adhesives and components of coatings (no limitations for Zinc Acetate specified) -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 -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 -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” -Zinc Acetate is GRAS as a trace mineral added to animal feeds using good feeding practice	21CFR175.105 21CFR310.545 21CFR347.10 21CFR347.50 21CFR582.80
Zinc Carbonate	-Indirect food additive, paper and paperboard components; Zinc Carbonate may be used as a colorant only -Ingredient food additives, polymers, rubber articles; Zinc Carbonate may be used as a filler -Indirect food additives; adjuvants, production aids, and sanitizers; Zinc Carbonate may be used as a colorant for polymers -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 -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 -Zinc Carbonate is GRAS as a trace mineral added to animal feeds using good feeding practice	21CFR176.170 21CFR177.2600 21CFR178.3297 21CFR310.545 21CFR347.10 21CFR582.80
Zinc Chloride	-Zinc Chloride is GRAS as a substance migrating to food from cotton and cotton fabrics in dry food packaging -Zinc Chloride is GRAS as a nutrient used for human consumption when used with GMP -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 -Zinc Chloride is GRAS as a trace mineral added to animal feeds using good feeding practice	21CFR182.70 21CFR182.8985 21CFR310.545 21CFR582.80; 21CFR582.5985
Zinc Gluconate	-Zinc Gluconate is GRAS as a nutrient used for human consumption when used with GMP -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 -Zinc Gluconate is GRAS as a nutrient or dietary supplement for animals when using GMP or feeding practice	21CFR182.8988 21CFR522.2690 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
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

(continued)

Table 7. (continued)

Ingredient	Non-Cosmetic Use	References
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) $\leq 0.3\%$ by weight in these polymers	21CFR178.2010
Zinc Stearate	-Indirect food additive, paper and paperboard components -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 -Indirect food additive; Zinc Stearate may be used as antioxidant and/or stabilizer in polymers -Zinc Stearate is GRAS as a nutrient used for human consumption when used with GMP -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 -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." -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 -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)	21CFR176.180 21CFR177.1460; 21CFR177.1900; 21CFR177.2410 21CFR178.2010 21CFR182.8994 21CFR310.545 21CFR369.20 21CFR582.5994 29CFR1910.1000; 29CFR1915.1000
Zinc Sulfate	-Zinc Sulfate is GRAS as a substance migrating to food from paper and paperboard products in food packaging -Zinc Sulfate is GRAS as a nutrient used for human consumption when used with GMP -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 -Ophthalmic drug products for OTC human use; Zinc Sulfate (0.25%) may be used as an active ingredient in ophthalmic astringents -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 -Zinc Sulfate (hydrated or anhydrous forms) is GRAS as a trace mineral added to animal feeds using good feeding practice	21CFR182.90 21CFR182.8997 21CFR310.545 21CFR347.50 21CFR558.258 21CFR582.80; 21CFR582.5997
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.

Health Organization (WHO) lists Zinc Sulfate (20 mg solid form, or 8.1 mg as free zinc (if not a hydrate)) as an oral administration drug used to treat diarrhea in children.³⁵

The following zinc salts are FDA approved for use in some OTC drug products: Zinc Acetate, Zinc Carbonate,

Zinc Sulfate, and Zinc Undecylenate. Zinc Acetate (0.1–2%) and Zinc Carbonate (0.2–2%) are approved as active ingredients in OTC skin protectants drugs. [21CFR347.10] It is recommended that Zinc Stearate dusting powders carry the warning: "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 has occupational air contaminant limitations according to Title 29 of the CFR (This information is summarized in 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.³⁹ Zinc Carbonate is used as an inactive ingredient in an FDA approved drug product to be delivered subcutaneously (0.16% powder for injection suspension).⁴⁰ Zinc Chloride is listed as an inactive ingredient in FDA approved drug products to be administered orally (7 mg, or 3.4 mg as free zinc), subcutaneously (0.006%), intradermally (0.7%), or in ophthalmic solutions (0.003% w/v).⁴¹ Zinc Stearate is used as an inactive ingredient in FDA approved drug products administered orally (2.04 mg to 36 mg, or, 0.21 mg to 3.72 mg as free zinc) and dermally (6% in an emulsion cream).⁴² Zinc Sulfate is used as an inactive ingredient in FDA approved drug products for oral administration (3.5 mg in a tablet, or 1.4 mg as free zinc).⁴³

Zinc Acetate is listed as an ingredient in a wound dressing approved by the FDA as a legally marketed predicate medical device.⁴⁵ Zinc Chloride (concentration not specified) has been reported to be used in a wound cream⁴⁴ and wound cleanser⁴⁶ and Zinc Gluconate (0.02%) was listed as an active ingredient (breath freshener) in a mouthwash⁴⁷ 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.⁸²

For animals, GRAS status was established in the U.S. for Zinc Acetate, Zinc Carbonate, Zinc Chloride, Zinc Gluconate, Zinc Stearate, and Zinc Sulfate with the use of good manufacturing and feeding practices (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.⁴⁹

Physiology and Biochemistry

Zinc is an essential trace mineral and is ubiquitous within every cell in the body.^{62,83} Zinc has a critical role as a structural component of proteins, an enzymatic co-factor, and transcriptional regulator in a wide array of cellular and biochemical processes. It regulates gene expression and intracellular signaling. Three percent of the human

genome consists of genes that encode zinc finger proteins. Zinc transporter gene regulation dominates all aspects of absorption and cellular zinc metabolism.

Zinc plays an important role in cell division.⁸⁴ In vertebrates, zinc is involved in neurotransmission, cell signaling, and immune response, as well as the metabolism of lipids, carbohydrates, proteins, and nucleic acids.⁴⁹ Zinc contributes to catalytic activity or the tertiary structure of proteins.

Although zinc is an essential nutrient, it can also be toxic.⁸⁵ Cells protect themselves from zinc toxicity by inducing proteins such as metallothionein (MT) that bind it tightly, by sequestering it in organelles, or by exporting it. MT, a 61-amino acid peptide rich in sulfur-containing cysteine residues, is the major intracellular binding protein for zinc.⁸³ There are four isotypes of MT proteins, with MT-1 and MT-2 present in all cells of the body. They regulate zinc [and copper] intracellular levels and flux and detoxify heavy metals; MTs are involved in nuclear transcription and play a role in immune function through their sequestration of metals. Higher zinc levels within the cell induce MT synthesis.

In addition to the chelating and releasing by MTs, mobilization of zinc across biological membranes is important to maintain cellular and subcellular zinc homeostasis.⁸⁶ Although zinc ions can cross biological membranes through various calcium channels, ZIP (Zrt- and Irt-like proteins) and zinc transporters (ZnT) transporter family proteins play crucial roles as transport routes.

Some organ systems are known to be clinically affected by severe zinc deficiency.⁸⁷ These systems include the central nervous, gastrointestinal, immune, epidermal, reproductive, and skeletal systems. This occurs due to increased requirements or excretion, inadequate dietary intake, conditioned deficiency, or genetic causes.

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 could amount to 1.6% because the amount retained in the skin should be regarded as being absorbed because it may become available at a later stage; 0.3% zinc was recovered in the receptor fluid (0.9% sodium chloride in double distilled water with antibiotics), and 1.3% zinc was recovered in the horny layer.³¹ 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.⁸⁸ In guinea

Table 8. Dermal Penetration Studies.

Test Substance(s)	Species	Sample Type or Test Population	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 (14.6 mg/mL of free zinc) in water, 1 mg/cm ² (0.26 mg/cm ² of free zinc) 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 double distilled water 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
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
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%

(continued)

Table 8. (continued)

Test Substance(s)	Species	Sample Type or Test Population	Results	Reference
Zinc Sulfate, Zinc Undecylenate (each labeled with 131 μ Ci/mole ^{65}Zn)	Rabbit	n=2 2.5 mg Zinc Sulfate (1.0 mg of free zinc) or 2.5 mg Zinc Undecylenate (0.378 mg of free zinc; 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	⁵⁸

PBS, Phosphate Buffered Saline; TEWL, transepidermal water loss.

pigs, <1% to 3.9% of 0.005–45.87M [^{65}Zn]-Zinc Chloride was absorbed in 5 h.⁸⁹ 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.⁵⁸

Absorption, Distribution, Metabolism, Excretion (ADME)

The majority of dietary zinc is absorbed in the upper small intestine.⁶² The luminal contents of the duodenum and jejunum, notably phytate, can have a major impact on the percentage of zinc that is available for absorption. With diets low in phytate and low in zinc, for example less than 4 mg/day, the fraction of zinc absorbed may be as high as 60% or more. The fraction of absorbed zinc decreases progressively with increasing dietary zinc. Absorption of zinc by the enterocyte is regulated in response to the quantity of bioavailable zinc ingested.

Albumin is the major transporter of zinc in both portal and systemic circulation. Virtually no zinc circulates in a free ionized form, and the majority of total body zinc is in muscle and bone. Zinc uptake capacity by the human placenta is inversely related to maternal plasma zinc concentrations and increases with increasing gestational age.

The rapid turnover of plasma zinc reflects its exchange with all tissues and organs in the body. There is a rapidly exchanging pool of zinc that fully exchanges with zinc in plasma and accounts for about 10% of total body zinc. 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.^{63,79} Zinc can be reabsorbed from the small intestines.⁶²

ADME studies summarized below are 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

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

Test Substance(s)	Species/ Strain	Test Population	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	90
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	90
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 $\mu\text{g}/\text{mL}$ than 125 $\mu\text{g}/\text{mL}$ concentration in serum and coagulum at 0.5 h and 2 h; percent of absorbed ^{65}Zn activity in skin 6.1% (1.1 $\mu\text{g}/\text{mL}$) and 3.6% (125 $\mu\text{g}/\text{mL}$); ^{65}Zn activity detected in dermis (near hair follicles), panniculus carnosus, and epidermis	90
Oral						

(continued)

Table 9. (continued)

Test Substance(s)	Species/ Strain	Test Population	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Zinc Acetate (dihydrate)	Dog/ Beagle	n=6	0, 2, 4 mg/kg/day (0, 0.6, 1.19 mg/kg/day as free zinc)	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	⁹¹
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	⁹²

(continued)

Table 9. (continued)

Test Substance(s)	Species/ Strain	Test Population	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	⁵³
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)	¹⁹
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 $\mu\text{g}/\text{h}/\text{dL}$ (intragastric pH ≤ 3) and 378 $\mu\text{g}/\text{h}/\text{dL}$ (intragastric pH ≥ 5)	²⁴

(continued)

Table 9. (continued)

Test Substance(s)	Species/ Strain	Test Population	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
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	Treatment orally administered with evening meal for 3 mos 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)	94

LOAEL, Lowest Observed Adverse Effect Level; NOAEL, No Observed Adverse Effect Level.

Table 10. Acute Toxicity Studies.

Test Substance(s)	Species/ Strain	Test Population	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 (or, > 207 mg/kg as free zinc, no further details)	⁶³
Zinc Sulfate (heptahydrate)	Rat/ Wistar	n = 5/sex	2000 mg/kg (455 mg/kg as free zinc)	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 (or, > 455 mg/kg as free zinc); 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	^{19,25,31}
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 (734 mg/kg of free zinc); LD ₅₀ of 2460 mg/kg reported for Zinc Acetate (dihydrate, 732.8 mg/kg of free zinc)	²⁴
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	⁹⁵
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	⁹⁵
Zinc Lactate	Rat/ Wistar	n=5/sex/group	500 or 2000 mg/kg (water vehicle, between 134 mg/kg and 537 mg/kg as free zinc)	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 (> 134 mg/kg of free zinc) and < 2000 mg/kg (< 537 mg/kg of free zinc); 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	²⁵
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	⁹⁵
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	⁹⁵
Zinc Phosphate	Rat/ Wistar	n=?	5000 mg/kg	Animals dosed in accordance with OECD TG 401	LD ₅₀ > 5000 mg/kg (> 847 mg/kg as free zinc) reported; no mortality or observed toxicity	²²

(continued)

Table 10. (continued)

Test Substance(s)	Species/ Strain	Test Population	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
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 (> 198 mg/kg as free zinc) reported; no toxicity or mortality observed; body weight gain normal; no treatment-related macroscopic observations during necropsy	²⁶
Zinc Stearate	Rat	n=Not specified	Not specified	Procedures not provided	LD ₅₀ > 5000 mg/kg (> 517 mg/kg as free zinc)	⁶³
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	²⁵
Zinc Laurate	Rat	n = 3/sex (for both main and satellite studies)	5.08 ± 0.03 mg/L air; nominal concentration: 6.67 mg/L air	4 h nose-only exposure, in accord with OECD Guideline 436 (Acute Inhalation Toxicity: Acute Toxic Class Method); MMAD 1.953 µm (GSD: 2.94) Main study – 14-day observation period; satellite study – 24 h observation period	LC ₅₀ > 5.08 mg/L air (actual concentration, or > 0.72 mg/L as free zinc); no animals died before study termination Gross changes in the nasal cavity and lungs include; marbled lungs observed in all animals of the main study (and in all satellite animals); small black foci were observed in 2 of 3 male and 1 of 3 female satellite animals	³³
Zinc Sulfate	Dog	n=5	0.1% (1.8–8.3 mg/m ³ , or, 0.7–3.0 mg/m ³ as free zinc) and 1% (15.8 mg/m ³ , or 5.8 mg/m ³ as free zinc)	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	⁹⁶

(continued)

Table 10. (continued)

Test Substance(s)	Species/ Strain	Test Population	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
Zinc Sulfate	Dog	n=5	0.5% (8.3 mg/m ³ , or 3.0 mg/m ³ as free zinc)	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	⁹⁶
Zinc Sulfate	Sheep	n=6	0.1% (1.8 mg/m ³ or 0.7 mg/m ³ as free zinc)	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	⁹⁶
Zinc Sulfate	Sheep	n=5	0.5% (8.3 mg/m ³ , or 3.0 mg/m ³ as free zinc)	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	⁹⁶

GLP, Good Laboratory Practice; GSD, geometric standard deviation; LC₅₀, 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	Concentration/Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Zinc Acetate (dihydrate)	Rat/ Sprague- Dawley	n=10 females/ group	0, 160, 320, 640 mg/kg/day (or, 0, 48, 96, 191 mg/kg/day as free zinc. Sugar added to water vehicle for palatability)	3 mo	ANIMAL Oral 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 (48 mg/kg/day of free zinc) reported; 2 animals at 640 mg/kg/day level (191 mg/kg/day of free zinc) 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	24,97

(continued)

Table 11. (continued)

Test Substance(s)	Species/Strain	Test Population	Concentration/Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
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 (or, 68, 680, 6820 ppm as free zinc)	13 wk	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 (104 mg/kg/day as free zinc), ~479 mg/kg/day in females (109 mg/kg/day as free zinc)) reported; 4 animals died in 30,000 ppm group (6820 ppm as free zinc); 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; polychromatophilia 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 (680 ppm as free zinc); slight, but reversible reduction in weight gain in females (300 ppm) after 1 week Rat results: NOEL of 3000 ppm (680 ppm as free zinc); 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 (6820 ppm as free zinc); 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 30,000 ppm); reduced calcium (in females at 3000 ppm and 30,000 ppm); relative and absolute organ weight fluctuations, but unclear if treatment-related; treatment-related pancreatic lesions observed (30,000 ppm)	21,98

(continued)

Table 11. (continued)

Test Substance(s)	Species/Strain	Test Population	Concentration/Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Zinc Sulfate (heptahydrate)	Rat/ Wistar Kyoto	n=12/group	Filtered air or 10, 30, or 100 µg/m ³ water soluble Zinc Sulfate (or, 2.3, 6.8, and 23 µg/m ³ as free zinc, particle size 30–43 nm)	16 wks	Inhalation 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 bronchoalveolar 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 or 23 µg/m ³ as free zinc) detected in gene array analysis test; plasma/serum markers unaffected by treatment; pathology revealed no pulmonary or cardiac changes as a result of treatment	93

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

was almost completely independent of the zinc concentration applied and the pH.⁹⁰

In oral studies, plasma, urinary, and blood zinc levels increased in dogs with increasing doses of Zinc Acetate.⁹¹ 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.⁹² In rats fed radiolabeled Zinc Carbonate, Zinc Chloride, and Zinc Chloride Hydroxide, the percent absorption of ⁶⁵Zn was similar with all three substances, ranging from 40% to 48%.⁵³ 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.¹⁹ 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.^{24,93} Following administration of 15 or 100 mg/day zinc, supplied as Zinc Acetate, to human subjects for 3 months, 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.⁹⁴

Toxicological Studies

Acute Toxicity Studies

The dermal LD₅₀ of an eye shadow formulation that contained 10% Zinc Stearate was >2 g/kg, or, as free zinc, >0.207 g/kg.⁶ The oral LD₅₀ of Zinc Stearate is >5 g/kg (>0.517 g/kg as free zinc) in rats. The inhalation LC₅₀ of Zinc Stearate following a single 1 h exposure was >200 mg/L (21 mg/L of free zinc) in rats; 1 animal died.

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

The dermal LD₅₀s of Zinc Stearate (in rabbits)⁶³ and Zinc Sulfate (heptahydrate, in rats)^{19,25,31} are >2000 mg/kg, or, as free zinc, >207 mg/kg and >455 mg/kg, respectively. Reported oral LD₅₀s are 287 mg/kg Zinc Acetate (dihydrate, 85 mg/kg as free zinc) in mice,⁹⁵ 794 mg/kg Zinc Acetate (dihydrate, 237 mg/kg as free zinc) in rats,⁹⁵ between 500 mg/kg (134 mg/kg of free zinc) and 2000 mg/kg (537 mg/kg of free zinc) Zinc Lactate in rats,²⁵ 926 mg/kg Zinc Nitrate (hexahydrate, 204 mg/kg as free zinc) in mice,⁹⁵ 1330 mg/kg Zinc Nitrate (hexahydrate, 292 mg/kg as free zinc) in rats,⁹⁵ > 5000 mg/kg Zinc Phosphate (>2141 mg/kg of free zinc) in rats,²² > 2000 mg/kg Zinc Ricinoleate (>198 mg/kg of free zinc) in rats,²⁶ and >5000 mg/kg Zinc Stearate (>517 mg/kg of free zinc) in rats.⁶³ In inhalation studies, reported LC₅₀s in rats are 2000 mg/m³ Zinc Chloride (959 mg/m³ of free zinc),²⁵ and >5.08 mg/L air Zinc Laurate (>0.72 mg/L of free zinc).³³ In dogs and sheep, inhalation exposure to ≤1.9 mg/m³ (1%) and ≤3.0 mg/m³ (0.5%) of free zinc from Zinc Sulfate, respectively, for up to 4 h did not

affect lung function (dogs) or tracheal mucous velocity (sheep).⁹⁶

Short-Term Toxicity Studies

In a 14-day dermal study in 6 guinea pigs, a significant increase in body weight was reported in animals dosed daily with an emulsion of Zinc Stearate (concentration not specified), egg yolk, and water.⁶

Subchronic Toxicity Studies

Subchronic toxicity studies summarized below are presented in Table 11.

In a 3-mo study in which 160–640 mg/kg/day Zinc Acetate (dihydrate, 48–191 mg/kg/day as free zinc) was added to drinking water of rats, a no-observed-effect-level (NOEL) of 160 mg/kg/day (48 mg/kg/day of free zinc) was reported; concentrations of zinc were statistically significantly higher in several organs and the blood of animals of the mid- and high-dose groups.^{24,97} In a 13-wk feed study of Zinc Sulfate, a NOEL of 3000 ppm (68 ppm as free zinc) was reported in mice and rats; some mice (but no rats) dosed with 30,000 ppm died (680 ppm as free zinc), and numerous toxic effects were reported in both mice and rats of the 30,000 ppm groups.^{21,98} No significant toxicologic effects or pulmonary or cardiac changes were reported in an inhalation study in rats exposed to 100 µg/m³ water soluble Zinc Sulfate (23 µg/m³ of free zinc) for 5 h/day for 3 days/week for 16 wks.⁹³

Developmental and Reproductive Toxicity (dart) Studies

Zinc is a very important element in the reproductive cycle of numerous species.⁹⁹ In humans, it is necessary for the formation and maturation of spermatozoa, for ovulation, and for fertilization. During pregnancy, zinc deficiency causes a number of anomalies: spontaneous abortion, pregnancy-related toxemia, extended pregnancy or prematurity, malformations, and retarded growth. Also, delivery is adversely affected by deficiency.

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 (149 or 298 mg/L as free zinc) 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 in the offspring.²⁴ In rats dosed by gavage with up to 30 mg/kg/day aq. Zinc Chloride (14 mg/kg/day of free zinc) for 84 days (prematuring 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

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

Test Substance(s)	Species/ Strain	Test Population	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Zinc Acetate	Mouse/ BALB/c	n= 30/group (sex distribution not specified)	500 or 1000 mg/L (149 or 298 mg/L as free zinc, 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	24
Zinc Chloride (99.99% purity)	Rat/ Sprague- Dawley	n=25/sex/group	0, 7.5, 15, 30 mg/kg/day (or, 0, 3.6, 7.2, 14.4 mg/kg/day as free zinc, 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 (3.6 mg/ kg/day of free zinc) 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 (3.6, 7.2, 14.4 mg/kg/day as free zinc), respectively	25,101

(continued)

Table 12. (continued)

Test Substance(s)	Species/ Strain	Test Population	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Zinc Chloride (99.99% pure)	Rat/ Sprague-Dawley	n=25/group	0, 7.5, 15, 30 mg/kg/day (or, 0, 3.6, 7.2, 14.4 mg/kg/day as free zinc, water vehicle)	Test substance administered daily by gavage; males and females dosed for 84 days through prenatation and lactation (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 (3.6 mg/kg/day of free zinc) treated females; statistically significant increase in stillbirths (15 and 30 mg/kg/day, or 7.2 and 14.4 mg/kg/day as free zinc); 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 prenatation phase, but males had statistically significant reduction in body weight (15 and 30 mg/kg/day groups) compared to controls in prenatation period; treated females showed statistically significant reduction in body weight during mating (30 mg/kg/day, or 14.4 mg/kg/day as free zinc), gestation (7.2 and 14.4 mg/kg/day zinc), 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 (7.2 and 14.4 mg/kg/day zinc); 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	100
Zinc Sulfate	Rat/ Wistar	n=25/group	0, 0.4, 2.0, 9.1, 42.5 mg/kg (or, 0, 0.1, 0.7, 3.3, 15.5 as free zinc, 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 (~16 mg/kg zinc equivalent) reported; no treatment-related effects observed	102
Zinc Sulfate	Rabbit/ Dutch	n=14–19/group	0, 0.6, 2.8, 13.0, 60.0 mg/kg (or, 0, 0.2, 1.0, 4.7, 22 mg/kg as free zinc, water vehicle)	Pregnant, female rabbits 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 (~22 mg/kg zinc equivalent) reported; no treatment-related effects observed; positive controls performed as expected	102

(continued)

Table 12. (continued)

Test Substance(s)	Species/ Strain	Test Population	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Zinc Sulfate (unspecified as to whether the anhydrous form or heptahydrate was used)	Hamster	n=23–25/group	0.9, 4.1, 19 and 88 mg/kg/day (0.4, 1.7, 7.7 and 35.5 mg Zn ²⁺ /kg for anhydrous form; or 0.2, 0.9, 4.3, 19.9 mg Zn ²⁺ /kg for heptahydrate form, respectively)	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	20,31
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 females mated with untreated males 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 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	21,103
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) compared 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	104
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 anhydrous 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	21

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.

fetal resorption.¹⁰⁰ In a two-generation reproduction toxicity study in which rats were dosed by gavage daily with up to 30 mg/kg/day aq. Zinc Chloride (14 mg/kg/day of free zinc), the overall no-observed-adverse-effect-level (NOAEL) was 7.5 mg/kg/day for the F₁ generation (3.6 mg/kg/day of free zinc).^{25,101} Parental animals from F₀ and F₁ generations had reduced fertility and viability, and effects on organ weights were reported in parental animals; reduced body weights were reported for F₁ and F₂ pups in 30 mg/kg/day group (14 mg/kg/day of free zinc), however no effects on weaning index, sex ratio, or litter size observed. The developmental and reproductive effects of Zinc Sulfate were examined in mice (≤ 30 mg/kg/day, or ≤ 6.8 mg/kg/day as free zinc (assuming the heptahydrate); days 6–15 of gestation),²¹ rats (up to 42.5 mg/kg, or ≤ 9.7 mg/kg/day as free zinc; days 6–15 of gestation),¹⁰² hamsters (≤ 88 mg/kg/day, or ≤ 35.6 mg/kg/day of free zinc; days 6–10 of gestation),^{20,31} and rabbits (≤ 60 mg/kg, or ≤ 13.6 mg/kg/day as free zinc; days 6–18 of gestation)¹⁰²; no developmental effects were observed. In studies in which male rats were fed a diet containing 4000 ppm zinc as Zinc Sulfate,^{21,103} 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.¹⁰⁴

Genotoxicity

Genotoxicity studies summarized below are described 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 $\mu\text{g}/\text{plate}$, or ≤ 2145 $\mu\text{g}/\text{plate}$ as free zinc),¹⁰⁵ unscheduled DNA synthesis (UDS) assay in rat hepatocytes (≤ 1000 $\mu\text{g}/\text{mL}$, or ≤ 298 $\mu\text{g}/\text{mL}$ of free zinc), and in human lymphocytes,¹⁰⁶ but it was positive in a mouse lymphoma assay in a dose-dependent manner (1.3–13 $\mu\text{g}/\text{mL}$ without and 4.2–42 $\mu\text{g}/\text{mL}$ with metabolic activation, or, 0.39–3.87 $\mu\text{g}/\text{mL}$ as free zinc without and 1.25–12.5 $\mu\text{g}/\text{mL}$ as free zinc with metabolic activation, respectively)¹⁰⁵ and in a chromosomal aberration assay in Chinese hamster ovary (CHO) cells (25–45 $\mu\text{g}/\text{mL}$ without and 45–80 $\mu\text{g}/\text{mL}$ with metabolic activation, or, 7.45–13.4 $\mu\text{g}/\text{mL}$ as free zinc without and 13.4–23.8 $\mu\text{g}/\text{mL}$ as free zinc with metabolic activation, respectively). Zinc Chloride was not mutagenic in an Ames test (≤ 100 mg/L, or ≤ 48 mg/L as free zinc),¹⁰⁷ a mouse lymphoma assay (≤ 12.13 $\mu\text{g}/\text{mL}$, or ≤ 5.8 mg/L as free zinc),¹⁰⁸ or chromosomal aberration assay in human dental pulp cells (≤ 300 μM , or ≤ 19.5 $\mu\text{g}/\text{mL}$ as free zinc)⁸²; it was genotoxic in a clastogenicity study in human peripheral blood leukocytes¹⁰⁹ and in a micronucleus assay with human

peripheral blood lymphocytes (at 100 mg/L, or at 47.6 mg/L as free zinc),¹⁰⁷ it was positive in a cytokinesis-block micronucleus assay,¹¹⁰ and 3.2 mM (208 $\mu\text{g}/\text{mL}$ of free zinc) caused a 2-fold increase in λ -prophage induction in *Escherichia coli* WP2 as compared to controls.²⁵ Zinc Nitrate (≤ 1 mM, or ≤ 65 $\mu\text{g}/\text{mL}$ as free zinc),¹¹¹ Zinc Stearate (concentrations not specified),²⁷ and Zinc Sulfate (≤ 3600 $\mu\text{g}/\text{plate}$, or ≤ 1312 $\mu\text{g}/\text{plate}$ as free zinc)²¹ 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 *Saccharomyces cerevisiae* diploid strain D4.²⁸ 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, or ≤ 7.2 mg/kg as free zinc),¹¹² in sperm-head abnormalities (≤ 15 mg/kg, or ≤ 7.2 mg/kg as free zinc), and in a Comet assay (eukaryotic cells; ≤ 19.95 mg/kg, or ≤ 9.6 mg/kg as free zinc).¹¹³

Carcinogenicity

Animal

Chester Beatty mice were administered Zinc Sulfate (heptahydrate; 1000 ppm and 5000 ppm, or, as free zinc, 227 ppm and 1135 ppm, respectively) 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).⁶³ There were no increased incidences for any neoplastic end points.

Other Relevant Studies

Transformation

Zinc Chloride. A transformation assay was performed using cells from Syrian hamster embryos (cryopreserved at day 14 of gestation).¹¹⁴ 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 , or 1.43 $\mu\text{g}/\text{mL}$ as free zinc) 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.

Table 13. Genotoxicity Studies.

Test Substance(s)	Species/Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
IN VITRO					
Zinc Acetate	<i>Salmonella typhimurium</i> TA1535, TA1537, TA1538, TA98, TA100	50 to 7200 µg/plate (15 to 2145 µg/plate as free zinc)	Ames test conducted with and without metabolic activation	Negative	105
Zinc Acetate	Mouse lymphoma cells (L5178Y)	1.3, 1.8, 2.4, 3.2, 4.2, 5.6, 7.5, 10, 13 µg/mL (0.39–3.87 µg/mL as free zinc) without metabolic activation; 4.2, 5.6, 7.5, 10, 13, 18, 24, 32, 42 µg/mL (1.25–12.5 µg/mL as free zinc) 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	105
Zinc Acetate	Chinese hamster ovary cells	25, 34, 45 µg/mL (7.45–13.4 µg/mL as free zinc) without metabolic activation; 45, 60, 80 µg/mL (13.4–23.8 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	105
Zinc Acetate	Rat hepatocytes	10 to 1000 µg/mL (2.98 to 298 µg/mL as free zinc)	Unscheduled DNA synthesis test conducted	Negative	105
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 (6.5 ng/mL to 65 µg/mL as free zinc)	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	106

(continued)

Table 13. (continued)

Test Substance(s)	Species/Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Zinc Acetate, Zinc Chloride, Zinc Sulfate	Human leucocytes	1.5×10^{-3} , 3.0×10^{-4} , 3.0×10^{-5} M zinc supplied as Zinc Acetate, Zinc Chloride, Zinc Sulfate (97.5, 19.5, 1.95 µg/mL of free zinc; 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; 3.0×10^{-4} (19.5 µg/mL of free zinc) and 3.0×10^{-5} M (1.95 µg/mL of free zinc) 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	61
Zinc Chloride	Mouse L5178Y/TK ⁺ lymphoma cells	1.21 to 12.13 µg/mL (0.58 to 5.82 as free zinc) 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	108
Zinc Chloride (99.9% pure)	Human dental pulp cells (D824 cells)	30, 100, 300 µM (1.95, 6.5, 19.5 µg/mL as free zinc)	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	82
Zinc Chloride	Human peripheral blood leucocytes	1.5×10^{-3} , 3.0×10^{-4} , 3.0×10^{-5} M zinc supplied as Zinc Chloride (97.5, 19.5, 1.95 µg/mL as free zinc)	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 (1.5×10^{-3} M lethal at 48 and 72 h, 97.5 µg/mL of free zinc); statistically significant increase in chromosomal aberrations at 48 and 72 h with both 0 and 24 h inoculation periods for 3.0×10^{-4} (19.5 µg/mL of free zinc) and 3.0×10^{-5} M (1.95 µg/mL of free zinc) compared to controls; statistically significant decrease in mitotic index value at 48 and 72 h with both 0 and 24 h inoculation periods for 3.0×10^{-4} and 3.0×10^{-5} M compared to controls	109

(continued)

Table 13. (continued)

Test Substance(s)	Species/Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Zinc Chloride	<i>S. typhimurium</i> TA98, TA100	1, 10, 25, 100 mg/L (0.48, 4.8, 12, 48 mg/L as free zinc) with metabolic activation 1, 10, 25 mg/L (0.48, 4.8, 12 mg/L as free zinc) without metabolic activation (100 mg/L (48 mg/L as free zinc) cytotoxic without metabolic activation)	Ames test performed with and without metabolic activation as indicated; positive and negative controls used	Non-mutagenic; controls performed as expected	107
Zinc Chloride	Human peripheral blood lymphocytes	1, 10, 100 mg/L (0.48, 4.8, 48 mg/L as free zinc; 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 (48 mg/L of free zinc) 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 (0.48 and 4.8 mg/L as free zinc), 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	107
Zinc Chloride	Human leucocytes	1.5×10^{-4} and 3.0×10^{-4} M zinc supplied as Zinc Chloride (9.75 and 19.5 µg/mL as free zinc) 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	110
Zinc Chloride	<i>Escherichia coli</i> WP2	3.2 mM (208 µg/mL of free zinc)	Experiment conducted to determine if test substance caused DNA damage and induced a pleiotropic response in <i>E. coli</i> ; 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	25

(continued)

Table 13. (continued)

Test Substance(s)	Species/Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Zinc Chloride	Human lymphocyte cultures	0, 0.003M, 0.0003M or 0.00003M (0, 19.5, 19.5 or 1.95 µg/mL as free zinc)	0.003M (19.5 µg/mL of free zinc) used to evaluate cytotoxicity; 0.0003M or 0.00003M (19.5 or 1.95 µg/mL as free zinc) 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	Mitotic activity inhibited at 0.003M; Control results (48 h culture): 3 aneuploid cells, 0 cells in endoreduplication, 1 gap chromatid aberrations; 0.0003M (19.5 µg/mL of free zinc) results at time zero (48 h culture): 1 aneuploid cells, 0 cells in endoreduplication, 2 gap chromatid aberrations; 0.0003M (19.5 µg/mL of free zinc) 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 (1.95 µg/mL of free zinc) results at time zero (48 h culture): 4 aneuploid cells, 0 cells in endoreduplication, 3 gap chromatid aberrations, 1 dicentric chromosome aberrations; 0.00003M (1.95 µg/mL of free zinc) results at 24 h post-initiation (48 h culture): 4 aneuploid cells, 2 gap chromatid aberrations, 2 fragment chromosome aberrations; Control results (72 h culture): 2 aneuploid cells, 0 cells in endoreduplication, 3 gap chromatid aberrations; 0.0003M (19.5 µg/mL of free zinc) results at time zero (72 h culture): 3 aneuploid cells, 0 cells in endoreduplication, 0 structural aberrations; 0.0003M (19.5 µg/mL of free zinc) 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, 1 gap chromosome aberrations	180

(continued)

Table 13. (continued)

Test Substance(s)	Species/Strain or Sample Type	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
Zinc Chloride	<i>S. typhimurium</i> TA97	0, 15.62, 31.25, 62.50, 125, 250.5, 500, 1000 μM /plate (1.0 to 65 $\mu\text{g}/\text{mL}$ of free zinc/plate) for preincubation tests without inhibitor; 18.75, 37.5, 75, 150, 300 μM /plate (1.2 to 19.5 $\mu\text{g}/\text{mL}$ of free zinc/plate) for preincubation tests with inhibitor; 0, 75, 150, 200, 300 μM /plate (4.9 to 19.5 $\mu\text{g}/\text{mL}$ of free zinc/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 , $\text{NaNH}_4\text{HPO}_4$, 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 (65 $\mu\text{g}/\text{mL}$ of free zinc/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	181
Zinc Nitrate (hexahydrate)	<i>S. typhimurium</i> TA98, TA100	0.01 mM and 1 mM (0.65 and 65 $\mu\text{g}/\text{mL}$ of free zinc)	Ames test performed with and without metabolic activation (S9 mix)	Negative	111
Zinc Stearate	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100; <i>Saccharomyces cerevisiae</i> strain 04	Range of test concentrations used based on 50% survival value, however concentrations used not specified (dimethyl sulfoxide, water, or saline vehicles)	A bacterial reverse mutation assay was performed with and without metabolic activation; water, saline, and positive controls used	Non-mutagenic	27
Zinc Sulfate	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100, TA1538	5 concentrations up to 3600 $\mu\text{g}/\text{plate}$ (1312 $\mu\text{g}/\text{plate}$ as free zinc, 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	21

(continued)

Table 13. (continued)

Test Substance(s)	Species/Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Zinc Sulfate	<i>S. cerevisiae</i> diploid strain D4	5000 ppm (2025 ppm as free zinc)/ 1000 ppm (405 ppm as free zinc; 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-convergentic	28
IN VIVO					
Zinc Chloride	Mouse/ C57Bl; 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	182
Zinc Chloride	Mouse/ Swiss albino; n = 5/ group	7.5, 10, 15 mg/kg (3.6, 4.8, 7.2 mg/kg as free zinc)	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	112
Zinc Chloride	Mouse/ Swiss albino; n = 5/ group	7.5, 10, 15 mg/kg (3.6, 4.8, 7.2 mg/kg as free zinc)	Dosage administered via intraperitoneal injection 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	112
Zinc Chloride	Mouse/ Swiss albino; n = 5/ group	2.0, 3.0 mg/kg (0.96, 1.44 mg/kg as free zinc)	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	112
Zinc Sulfate	Mouse/ Swiss albino, n=6 males/group	0, 5.7, 8.55, 11.40, 14.25, 17.10, 19.95 mg/kg (0, 2.3, 3.5, 4.6, 5.8, 6.9, 8.1 mg/kg as free zinc, 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	113

HEPES buffer = (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), zwitterionic biological buffer pH 6.8–8.2. ¹⁸³

Another transformation assay conducted in Syrian hamster embryo cells (13 to 14 days into gestation) showed that Zinc Chloride (up to 20 $\mu\text{g/mL}$ of appropriate medium, or, up to 9.6 $\mu\text{g/mL}$ as free zinc) 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%.¹¹⁵ 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.¹¹⁶ 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.

Zinc Sulfate. An *in vitro* screening assay in serum-free culture medium was conducted to determine whether 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.¹¹⁷ 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.¹¹⁶ Olfactory sensory neurons were damaged in treated mice: the mice were not able to detect odorants during behavioral testing approximately 1 week post-treatment and no recovery of function was observed by 2 months post-treatment. 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 Pigmentation

Zinc Sulfate. The effects of Zinc Sulfate on murine hair follicle melanogenesis were evaluated in an oral exposure

experiment.¹¹⁸ C57BL/6a/a mice were administered up to 20 mg/mL (~1200 mg/kg) Zinc Sulfate (heptahydrate, 273 mg/kg as free zinc) 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 pheomelanogenesis. 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

Zinc Chloride. The effects of Zinc Chloride on corneal wound healing were evaluated in male Wistar rats with corneal abrasion.¹¹⁹ 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 mm² 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

The dermal irritancy of 6 zinc compounds was examined in 3 animal models.² In open patch tests involving 5 daily applications, aqueous Zinc Acetate (20%) was found to be severely irritating in rabbit, guinea-pig, and mouse tests, inducing epidermal hyperplasia and ulceration. Epidermal irritancy in these studies was reportedly related to the interaction of zinc ion with epidermal keratin.

A trade name mixture that generally contains >50% Zinc Ricinoleate was applied (mixture applied at 10%; $n = 6$) to intact and abraded skin for 24 h under occlusive patches and

after patch removal.⁵ Well-defined erythema was observed at 48 and 72 h at the abraded sites of all six rabbits and at the intact sites of four rabbits. This mixture did not produce skin sensitization in a study involving 30 white guinea pigs.

Application of an occlusive patch containing 0.5 g undiluted Zinc Stearate (0.05 g zinc equivalent) for 4 h was not irritating to rabbit skin ($n = 6$).⁶ An eye shadow formulation containing 10% Zinc Stearate was not irritating to rabbit skin. Eye shadow formulations containing 10% Zinc Stearate were not irritants or sensitizers in a Schwartz-Peck prophetic patch test ($n = 202$ subjects) or a Draize-Shelanski repeated insult patch test (RIPT; $n = 99$ subjects).

A summary of dermal irritation and sensitization studies is provided below, and details are presented in Table 14. Summary information on irritation and sensitization of constituent acids previously reviewed by the Panel is provided in Table 2.

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. These 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 Chloride were severely irritating and Zinc Sulfate and Zinc Undecylenate were slightly irritating.¹²⁰ Four h patches of Zinc Lactate (final concentration not reported; occlusive),²⁵ Zinc Neodecanoate (undiluted; semi-occlusive),²⁹ Zinc Ricinoleate (undiluted; occlusive),²⁶ and Zinc Sulfate (final concentration not reported; semi-occlusive)³¹ were non-irritating to rabbit skin. A single application of Zinc Nitrate (concentration not reported) resulted in pronounced skin irritation in rats, rabbits, and guinea pigs; details were not provided.³² In clinical testing, Zinc Gluconate (0.05% in formulation)¹²¹ and Zinc Undecylenate (0.25% in formulation)¹²² were non-irritating.

In a mouse local lymph node assay, a 10% solution of Zinc Sulfate was non-sensitizing.^{25,123} 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.⁶³ Zinc Chloride (in formulation, effective test concentrations of 0.229%¹²⁴ and 0.326%¹²⁵; $n = 55$ and 52, respectively), Zinc Laurate (7% in formulation; $n = 104$),¹²⁶ and Zinc Myristate (in formulation, effective test concentration 14%; $n = 49$)¹²⁷ were not irritants or sensitizers in human repeated insult patch tests (HRIPTs).

Ocular Irritation

Undiluted Zinc Stearate was non- to minimally irritating to rabbit eyes.⁶

The ocular irritation studies that are summarized below are presented in Table 15. Summary information on ocular irritation of constituent acids previously reviewed by the Panel is provided in Table 2.

In *in vitro* studies, Zinc Acetate (97%) was corrosive in an isolated chicken eye test,²⁴ In an EpiOcular™ assay, Zinc Laurate (7.64% in formulation) had an exposure time that induces a 50% reduction in viability, relative to the negative control (t_{50}) of >24 h, compared to the positive control value of 32.5 min,¹²⁸ and Zinc Citrate (undiluted powder) was considered an irritant in a reconstructed human cornea-like epithelium test.²³ In rabbit eyes, Zinc Phosphate (concentration not reported)²² and Zinc Ricinoleate (concentration not reported)²⁶ were non-irritating, Zinc Nitrate (concentration not reported) was irritating,³² Zinc Lactate (undiluted powder) was very irritating,²⁵ and Zinc Sulfate (undiluted) was severely irritating.^{30,31}

Clinical Studies

Prospective Studies

Zinc Chloride. In humans, inhalation exposure via aerosol (exposure duration not specified) to 40 mg/m³ Zinc Chloride (19.2 mg/m³ of free zinc) produced a metallic taste; the particle size and other details were not provided.⁶³ Another study reported that in human subjects exposed via inhalation to 4800 mg/m³ Zinc Chloride (2302.5 mg/m³ of free zinc) for 30 minutes, pulmonary effects were induced (no further details).

Zinc Laurate. The fractional deposition in human respiratory tract (multiple-path particle dosimetry (MPPD) model, based on calculated MMAD) is 60.2% head, 1.8% tracheobronchial, and 5.6% pulmonary.³³

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,¹²⁹⁻¹³¹ but not all,¹³² of the studies (Table 16).

Case Reports

Inhalation. Cases of adverse effects following occupational inhalation exposure, and severe effects in infants (including death) that inhaled Zinc Stearate powder, were reported.⁶

Zinc Chloride. There are case reports involving slowly progressing adult respiratory distress syndrome (~10 to 32 days post-exposure),¹³³ sometimes resulting in death, after inhalation of Zinc Chloride from a smoke bomb.¹³³⁻¹⁴⁰ In a case where a patient survived, corticosteroid treatment and extracorporeal life support measures were followed.¹³⁴

Table 14. Dermal Irritation and Sensitization Studies.

Test Substance(s)	Species/Strain	Test Population-	Concentration (Vehicle)	Procedure	Results	Reference
IRRITATION						
Animal						
Zinc Chloride, Zinc Sulfate, Zinc Undecylenate (purity of above zinc salts $\geq 98\%$)	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: 1% (w/v) Zinc Chloride (deionized water vehicle); Group 2: 1% (w/v) Zinc Sulfate (deionized water); Group 3: 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 5 th 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 5 th 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 5 th treatment day animals killed Histology (all animals) and epidermal cell kinetics (mouse only) performed Test substance applied 1 x/day for 5 days to dorsal skin; non-invasive mexametry using multiprobe adapter system utilized for erythema evaluation	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 Chloride, and Zinc Sulfate (less frequently) detected in superficial skin layers (bound to epidermal keratin) of all animals Epidermal cell kinetics test showed Zinc Chloride induced epidermal hyperplasia; Zinc Sulfate and Zinc Undecylenate performed similarly to controls	¹²⁰
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	¹⁸⁴
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	¹⁹

(continued)

Table 14. (continued)

Test Substance(s)	Species/Strain	Test Population-	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 5 cm 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	30
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 (0.13 g zinc equivalent) 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	25
Zinc Neodecanoate	Rabbit/ Himalayan	n=3	Undiluted	0.5 ml test substance applied to 6 cm 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	29
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)	32
Zinc Ricinoleate	Rabbit/ New Zealand White	n=6	Solid powder (undiluted, no vehicle)	0.5 g test substance (0.05 g zinc equivalent) 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	26
Zinc Sulfate	Rabbit/ New Zealand White	n=3	Zinc Sulfate, moistened, but no vehicle used (no further details provided)	0.5 g test substance (0.2 g zinc equivalent) 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	31
Human Zinc Gluconate	Human	n=11	0.05% in a face and neck cream	A single application of 25 µL of test substance applied on scapular back for 48 h; occlusive (Finn chamber) patch; skin examined 30 min and 24 h post-patch removal	Non-irritating	121
Zinc Stearate	Human	n=20	3% in an eye shadow	Clinical test to evaluate tolerability and safety on periocular area; applied daily for a month; 50% of volunteers wore contact lenses	Non-irritating to palpebral skin and mucosa	185

(continued)

Table 14. (continued)

Test Substance(s)	Species/Strain	Test Population-	Concentration (Vehicle)	Procedure	Results	Reference
Zinc Undecylate	Human	n=10	0.25% in a foot powder	A single application of 0.0212 g (0.0032 zinc equivalent) applied on the arm for 48 h; occlusive (Finn chamber) patch; skin examined 30 min post-patch removal	Non-irritating	122
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)	25,123
Zinc Sulfate	Guinea Pig	n = 10 treated; n = 5 controls	Intradermal induction: 0.1% Epidermal induction: 50% Challenge: 50% (pre-treatment with 10% sodium dodecyl sulfate)	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	63
Human						
Zinc Chloride	Human	n=55	0.327% in a foundation, tested at 70% in squalene (test concentration 0.229% % Zinc Chloride)	HR IPT; 24-h occlusive patches with approximately 0.1–0.15 g test material were applied 3x/wk for 3 wks; challenge patch applied after a 2-wk non-treatment period	Not an irritant or sensitizer	124
Zinc Chloride	Human	n=52	0.465% in a face powder, tested at 70% in squalene (test concentration 0.326% Zinc Chloride)	HR IPT; 24-h occlusive patches with approximately 25–38 mg/cm ² test material were applied 3x/wk for 3 wks; challenge patch applied after a 2-wk non-treatment period	Not an irritant or sensitizer	125
Zinc Laurate	Human	n=104	7% in a blush formulation	HR IPT; 20 mg applied neat using Finn chambers with a 50 mm ² inner surface	Not an irritant or sensitizer	126
Zinc Myristate	human		20% in a powder product (tested at 70% in squalene) (test concentration 14% Zinc Myristate)	HR IPT; 24-h occlusive patches with approximately 25–38 mg/cm ² test material were applied 3x/wk for 3 wks; challenge patch applied after a 2-wk non-treatment period	Not an irritant or sensitizer	127

EU, European Union; GLP, Good Laboratory Practice; HR IPT, 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	Concentration (Vehicle)	Procedure	Results	Reference
IN VITRO						
Zinc Acetate (97%)	Chicken	n=3 eyeballs/group	0.03 g (0.011 g zinc equivalent, 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	²⁴
Zinc Citrate	N/A	Human corneal tissue (three- dimensional model)	Particulate powder (no vehicle)	50.4 mg test substance (17.2 mg zinc equivalent) 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%)	²³
Zinc Laurate	N/A	Human cell construct	7.64% in a brush powder	Tissue equivalent assay with EpiOcular™ cultures; negative and positive controls used. A MTT time range-finding study was performed with times of 1, 4, 8, and 16 h; because of the dark color of the test article, a killed control experiment was performed in the time range-finding assay. A definitive assay was then performed with 16, 20, and 24 h exposure times	The killed control experiment demonstrated that the test article did not have a significant effect on final MTT results. In the definitive assay, the "t ₅₀ " of the positive control and the test article were 35.5 min and >24 h, respectively	¹²⁸
IN VIVO						
Zinc Lactate	Rabbit/ New Zealand White	n=3	Solid powder (unchanged, no vehicle)	0.1 g test substance (0.027 g zinc equivalent) instilled into lower right fornix 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	²⁵
Zinc Nitrate (hexahydrate)	Rabbit	n=?	Concentration not specified	Procedures not provided	Irritating; study author's reported dimness of cornea, mucous membrane ulceration, and cicatricial alterations in eyelids	³²
Zinc Phosphate (Tetrahydrate)	Rabbit/ New Zealand White	n=3	100 mg (42.8 mg zinc equivalent, 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 conjunctivae and chemosis noted within 48 h post-application; no iris or corneal lesions or conjunctival discharge observed	²²
Zinc Ricinoleate	Rabbit/ New Zealand White	n=6	White powder (no vehicle)	0.1 g test substance (0.01 g zinc equivalent) 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	²⁶
Zinc Sulfate	Rabbit/ New Zealand White	n=3 males	Unchanged (no vehicle)	~ 98.1 mg test substance (39.7 mg zinc equivalent) 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	^{30,31}

GLP, Good Laboratory Practice; MTT, 3[4,5-dimethylthiazol-2-yl]-diphenyltetrazolium bromide; 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 (4.0 mg zinc equivalent)	Test substance administered daily on average beginning week 25 of gestation; study was blind, randomized; controls did not receive treatment	Fewer 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	¹²⁹
Zinc Citrate	n=13 pregnant women in treatment group; n=16 pregnant women in control group; treatment and control patients were compliant	100 mg Zinc Citrate equivalent to 34.2 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; Cesarean 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	¹³⁰
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 11 subjects 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	¹³¹

(continued)

Table 16. (continued)

Test Substances(s)	Test Population	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
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	132

There is a report of a patient with permanent anosmia after splashing a Zinc Chloride solution into his nasal passages (no further details provided).⁶³

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.¹⁴¹ The patient had dental fillings installed 3 months 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 adults¹⁴²⁻¹⁴⁴ and children.¹⁴⁵⁻¹⁴⁸ 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).¹⁴² 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.¹⁴⁵⁻¹⁴⁷ 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 antropyloplasty with an uneventful recovery, although on follow-up delayed gastric emptying was noted.¹⁴⁶ Chelation therapy in children and adults was initiated if systemic toxicity persisted or when serum zinc levels were elevated.^{144,145,147,148}

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.¹⁴⁹ 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.⁶³

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).³⁴

Epidemiological Studies

Numerous epidemiological studies, including case-control, cohort and randomized clinical trials, have shown mixed results in regard to the association between zinc intake and prostate cancer risk.¹⁵⁰ A systematic review and meta-analysis was conducted using 17 studies of these studies (including 3 cohorts, 2 nested case-control, and 11 case-control studies, and 1 randomized clinical trial); 12 studies were included in a dose-response meta-analysis. In the dose-response meta-analysis, a non-linear trend in the relationship between zinc intake and prostate cancer was observed; there was no evidence for an association between zinc intake and prostate cancer.

Summary

This report addresses the safety of 27 inorganic and organometallic zinc salts as used in cosmetic formulations. The ingredients named in this assessment are all zinc salts, specifically of the 2⁺ oxidation state cation of zinc (Zn (II)). According to the *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.

VCRP data obtained from the US FDA and data received in response to a survey of the maximum reported use concentration by product category conducted by the Council indicate that 19 of the 27 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). Several zinc salts are used in oral care products. Because it is possible for the incidental ingestion of zinc

through the use of these products, the concentration of zinc present via a zinc salt (determined using zinc salt formula weights) that is used in oral care products or lipsticks is also included in this report. The greatest reported concentration of zinc present in oral care products is 0.22% via Zinc Citrate in a dentifrice (reported to be used at up to 2%), and the greatest concentration of zinc present in lipstick is 0.61% via Zinc Myristate (reported to be used at up to 5%).

The European Commission restricts zinc from water soluble zinc compounds to a maximum of 1%. 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 US, 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 daily 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.

Zinc is an essential trace mineral and is ubiquitous within every cell in the human body. It has a critical role as a structural component of proteins, an enzymatic co-factor, and transcriptional regulator in a wide array of cellular and biochemical processes. Although zinc is an essential nutrient, it can also be toxic. Cells protect themselves from zinc toxicity by inducing proteins such as metallothionein that bind it tightly, by sequestering it in organelles, or by exporting it.

The majority of dietary zinc is absorbed in the upper small intestine. The luminal contents of the duodenum and jejunum can have a major impact on the percentage of zinc that is available for absorption. With diets low in phytate and low in zinc, the fraction of zinc absorbed may be as high as 60% or more. The fraction of absorbed zinc decreases progressively with increasing dietary zinc. Absorption of zinc by enterocytes is regulated in response to the quantity of bioavailable zinc ingested.

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 to 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 LD₅₀s of Zinc Stearate (in rabbits) and Zinc Sulfate (heptahydrate, in rats) are >2000 mg/kg, or, as free zinc, >207 mg/kg and >455 mg/kg, respectively. Reported oral LD₅₀s are 287 mg/kg Zinc Acetate (dihydrate, 85 mg/kg as free zinc) in mice, 794 mg/kg Zinc Acetate (dihydrate, 237 mg/kg as free zinc) in rats, between 500 mg/kg (134 mg/kg as free zinc) and 2000 mg/kg Zinc Lactate (537 mg/kg as free zinc) in rats, 926 mg/kg Zinc Nitrate (hexahydrate, 204 mg/kg as free zinc) in mice, 1330 mg/kg Zinc Nitrate (hexahydrate, 292 mg/kg as free zinc) in rats, >5000 mg/kg Zinc Phosphate (>2141 mg/kg as free zinc) in rats, >2000 mg/kg Zinc Ricinoleate (>198 mg/kg as free zinc) in rats, and >5000 mg/kg Zinc Stearate (>517 mg/kg as free zinc) in rats. In inhalation studies, the LC₅₀ of Zinc Chloride is 2000 mg/m³ (959 mg/m³ as free zinc) in rats. In dogs and sheep, inhalation exposure to ≤1.9 mg/m³ (1%) and ≤3.0 mg/m³ (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, 48–191 mg/kg/day as free zinc) was added to

drinking water of rats, a NOEL of 160 mg/kg/day (48 mg/kg/day of free zinc) 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 (68 ppm as free zinc) was reported in mice and rats; some mice (but no rats) dosed with 30,000 ppm died (680 ppm as free zinc), and numerous toxic effects were reported in both mice and rats of the 30,000 ppm groups. No significant toxicological effects or pulmonary or cardiac changes were reported in an inhalation study in rats exposed to 100 $\mu\text{g}/\text{m}^3$ water soluble Zinc Sulfate (23 $\mu\text{g}/\text{m}^3$ of free zinc) 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 months, 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 (149 or 298 mg/L as free zinc, respectively) 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 (14 mg/kg/day of free zinc) for 84 days (prematuring 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 (14 mg/kg/day of free zinc), the overall NOAEL was 7.5 mg/kg/day for the F₁ generation (3.6 mg/kg/day of free zinc). Parental animals from F₀ and F₁ generations showed reduced fertility and viability, and effects on organ weights were reported in parental animals; reduced body weights were reported for F₁ and F₂ 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, or ≤ 6.8 mg/kg/day as free zinc), rats (up to 42.5 mg/kg, or ≤ 9.7 mg/kg/day of free zinc), hamsters (≤ 88 mg/kg/day, or ≤ 35.6 mg/kg/day as free zinc), and rabbits (≤ 60 mg/kg, or ≤ 13.6 mg/kg/day as free zinc); 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 $\mu\text{g}/\text{plate}$, or ≤ 2145 $\mu\text{g}/\text{plate}$ as free zinc), UDS assay in rat hepatocytes (≤ 1000 $\mu\text{g}/\text{mL}$, or ≤ 298 $\mu\text{g}/\text{mL}$ as free zinc), and in human lymphocytes, but it was positive in a mouse lymphoma assay in a dose-dependent manner (1.3–13 $\mu\text{g}/\text{mL}$ without and 4.2–42 $\mu\text{g}/\text{mL}$ with metabolic activation, or, 0.39–3.87 $\mu\text{g}/\text{mL}$ as free zinc without and 1.25–12.5 $\mu\text{g}/\text{mL}$ as free zinc with metabolic activation, respectively) and in a chromosomal aberration assay in CHO cells (25–45 $\mu\text{g}/\text{mL}$ without and 45–80 $\mu\text{g}/\text{mL}$ with metabolic activation, 7.45–13.4 $\mu\text{g}/\text{mL}$ as free zinc without and 13.4–23.8 $\mu\text{g}/\text{mL}$ as free zinc with metabolic activation, respectively). Zinc Chloride was not mutagenic in an Ames test (≤ 100 mg/L, or ≤ 48 mg/L of free zinc), a mouse lymphoma assay (≤ 12.13 $\mu\text{g}/\text{mL}$, or ≤ 5.8 mg/L as free zinc), 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),¹¹¹ Zinc Stearate (concentrations not specified),²⁷ and Zinc Sulfate (≤ 3600 $\mu\text{g}/\text{plate}$, or ≤ 1312 $\mu\text{g}/\text{plate}$ as free zinc)²¹ were not mutagenic in the Ames test, and Zinc Sulfate was non-converting in a mitotic recombination assay performed with 4-h exposure duration in *Saccharomyces 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, or ≤ 7.2 mg/kg as free zinc), in sperm-head abnormalities (≤ 15 mg/kg, or ≤ 7.2 mg/kg of free zinc), and in a Comet assay (eukaryotes; ≤ 19.95 mg/kg, or ≤ 9.6 mg/kg as free zinc).

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 up to 1200 mg/kg (273 mg/kg of free zinc) in the drinking water of mice, resulted in a statistically significant 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 Gluconate (0.05% in formulation) and Zinc Undecylenate (.25% in formulation) were non-irritating.

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. Zinc Chloride (in formulation, effective test concentrations of 0.229 and 0.326% in 70% squalene; $n = 55$ and 52 , respectively), Zinc Laurate (7% in formulation; $n = 104$), and Zinc Myristate (in formulation, effective test concentration 14% in 70% squalene; $n = 49$) were not irritants or sensitizers in human repeated insult patch tests (HRIPTs).

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 an EpiOcular™ assay, Zinc Laurate (7.64% in formulation) had a “ t_{50} ” of >24 h, compared to the positive control value of 32.5 min. 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.

In humans, inhalation exposure via aerosol (exposure duration not specified) to 40 mg/m³ Zinc Chloride (19.2 mg/m³ of free 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/m³ Zinc Chloride (2302.5 mg/m³ of free zinc) 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 months 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.

Numerous epidemiological studies have shown mixed results in regard to the association between zinc intake and prostate cancer risk. In the dose-response meta-analysis, a non-linear trend in the relationship between zinc intake and prostate cancer was observed; there was no evidence for an association between zinc intake and prostate cancer.

Discussion

The ingredients in this report are being reviewed together because they are all zinc salts, specifically of the ²⁺ oxidation state cation of zinc (Zn (II)). The Panel has previously found many of the counter ions safe for use in cosmetics.

The majority of these zinc salts demonstrated little to no irritation potential; however, Zinc Chloride was reported to be severely irritating at 1%, and the threshold for irritation is not known. Therefore, the Panel was concerned that the potential exists for dermal irritation with the use of products formulated using Zinc Chloride. The Panel specified that products containing zinc salts must be formulated to be non-irritating.

The Panel noted that zinc salts are rapidly absorbed both dermally and from the gastrointestinal tract, and that zinc ingredients in oral care products would have high bioavailability. However, concern about systemic effects is mitigated by low use concentrations and by low toxicity of these ingredients in oral exposures.

In DART studies, administration of zinc salts by gavage before, during, and after gestation resulted in toxic effects in parental males and females, and in some studies adverse effects in reproductive and developmental systems. The Panel noted, however, that the levels of zinc used in such studies were at concentrations that were much higher than could be achieved by a topical application of a cosmetic product.

The Panel recognized that several genotoxicity tests on zinc salts gave mixed results. The weight of evidence indicates that the zinc salts are not genotoxic at concentrations below cytotoxic levels.

Mixed results have been obtained in epidemiology studies that have examined the association between zinc intake and the incidence of prostate cancer. The Panel determined that the weight of evidence in epidemiology studies did not associate exposure to zinc with the incidence of prostate cancer. Therefore, based on the low levels of exposure and strict regulation of homeostasis, as well as the available data and the meta-analysis, the Panel was not concerned about the risk of zinc in cosmetic products.

The Panel noted that Zinc Sulfate reduced hair shaft melanin content in an oral exposure study, and that hair shaft depigmentation was observed during multiple hair cycles in treated animals. However, the Panel noted that this study was conducted at high concentrations and therefore the results were not toxicologically significant to the safety of use in cosmetics.

The Panel expressed concern regarding heavy metals that may be present in zinc salts. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

Finally, the Panel discussed the issue of incidental inhalation exposure, as some of the zinc salts are used in cosmetic sprays and could possibly be inhaled. For example, Zinc Ricinoleate is used in deodorant aerosols at concentrations up

to 2.3%, and Zinc Myristate is used in face powders at up to 20%. The available inhalation data did not lead to any cause for concern. Additionally, the Panel noted that in aerosol products, most droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <https://www.cir-safety.org/cir-findings>.

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 27 zinc salts are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

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

* Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

Author's Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

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