Safety Assessment of Zinc Salts as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	February 9, 2018
Panel Meeting Date:	March 5-6, 2018

The 2018 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Laura N. Scott, former Scientific Writer/Analyst, and Monice Fiume, Senior Director.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Senior Director
Date: February 9, 2018
Subject: Safety Assessment of Zinc Salts as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of Zinc Salts as Used in Cosmetics. This report was reviewed for the first time at the December 2017 meeting. The Panel issued a tentative report for public comment with the conclusion that the 27 zinc salts included in this assessment are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

The Scientific Literature Review (SLR) that was issued for this group of ingredients included Zinc Sulfide. Because Zinc Sulfide is chemically different from the other ingredients included in this safety assessment (e.g., is not a dissociable salt), the Panel removed Zinc Sulfide from the report.

Recently, the CIR SSC proposed that Zinc Oxide should be added to the report. However, the bonds between zinc and oxygen therein bear considerable covalent character; covalent bonding was the rationale for excluding Zinc Sulfide from the report. These two chemicals also share in common the ability to form wurtzite (hexagonal) crystal structures. Does the Panel think Zinc Oxide should be included in this report?

Various new data items have been added to the report. The Council updated the concentration of use data to include the concentration of zinc present in oral care or lipstick formulations (*zincst032018data_1*). Also, as requested, physiology and biochemistry data have been included. Unpublished data were received; these HRIPTs studies on formulations containing Zinc Chloride, Zinc Laurate, and Zinc Myristate have been incorporated (*zincst032018data_2*). And finally, summary information on irritation and sensitization of constituent acids previously reviewed by CIR has been added, as requested; that information is found in Table 2. All new data are indicated by highlighting.

Several sets of comments have been received. Council comments were received prior to the December meeting and in response to the Tentative Report. Comments were also received from the CIR Science and Support Committee (2 sets), and from a Council member company of the SLR. These comments, which are included for your review, have mostly been addressed. The comments submitted from the CIR SSC on February 1 included some points that require additional time to address. Particularly, the meta-analysis on prostate cancer studies will be obtained. This will be provided in Wave 2.

Additionally, please review the CIR SSC comment (second submission) regarding the genotoxicity data, and provide feedback for inclusion in the Discussion of the report.

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The following files are included as a part of this report package:

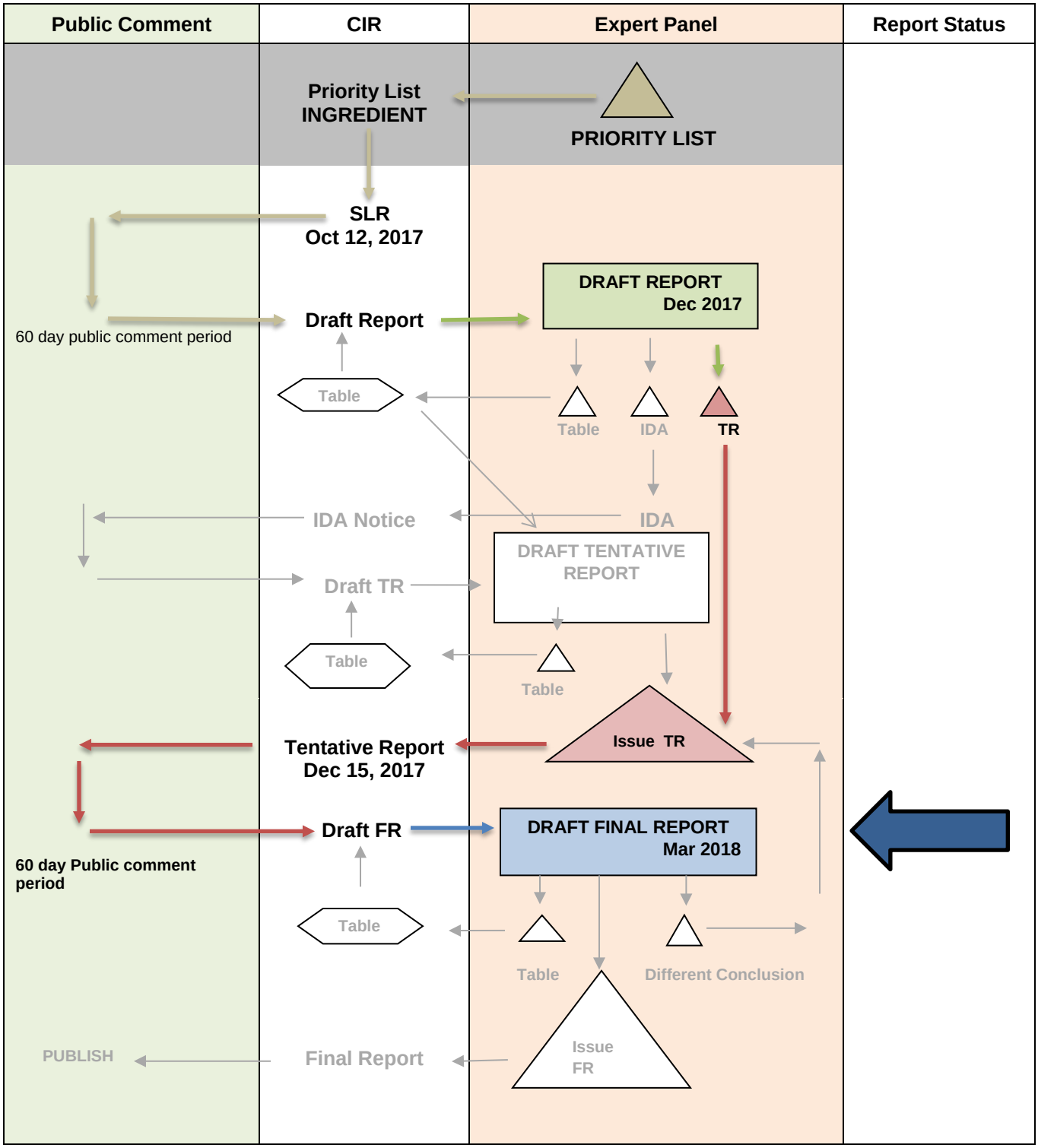
zincst032018flow:	report flowchart	*zincst032018data_2*:	described above
zincst032018hist:	report history	*zincst032018FDA*:	2017 VCRP data
zincst032018prof:	data profile	*zincst032018pcpc_1*:	comments on the SLR
zincst032018strat:	search strategy	*zincst032018pcpc_2*:	comments on the TR
zincst032018rep:	draft final report	*zincst032018CIRSCC_1*:	CIR SSC comments
zincst032018min:	minutes	*zincst032018CIRSCC_2*:	CIR SSC comments
zincst032018data_1:	described above	*zincst032018member comments*	

The Panel should carefully review the Abstract, Discussion, and Conclusion of this report, the submitted comments, and all new data. If these are satisfactory, the Panel should issue a final report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Zinc Salts

MEETING March 2018



History – Zinc Salts

SLR: announced Oct 12, 2017

Dec 4-5, 2017: Draft Report
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:

Zinc Acetate (2012)
Zinc Citrate (2014)
Zinc Myristate (2010)
Zinc Ricinoleate (2007)
Zinc Stearate (1982; reaffirmd in 2002)

Concentration of use data; skin irritation testing of formulations containing Zinc Gluconate, Zinc Stearate, and Zinc Undecylenate; and an EpiOcular™ study of a formulation containing Zinc Laurate were received and incorporated into the report.

The Panel removed an ingredient that was included in the original listing (and in the SLR). Because Zinc Sulfide is chemically different from the other ingredients included in this safety assessment (e.g., is not a dissociable salt), the Panel removed Zinc Sulfide from the report.

The Panel issued a tentative report for public comment with the conclusion that the 27 zinc salts are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

Mar 5-6, 2018: draft Final Report

Zinc Salts - – Mar 2018 – Monice Fiume
(X- new data; O- data were included in the original report)

	Reported Use - current	Method of Mfg	Impurities	ADME	Dermal Penetration	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhalation	Animal Tox – Rptd Dose, Dermal	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhalation	Animal Tox – Rptd Dose, Parenteral	DART	Genotoxicity	Carcinogenicity	Dermal Irritation	Dermal Sensitization	Phototoxicity	Case Reports	Ocular Irritation	Mucous Membrane Irr
Zinc Acetate	X	X	X	X			X			X			X	X		O				X	
Zinc Ascorbate	X																				
Zinc Ascorbate Hydroxide																					
Zinc Aspartate	X																				
Zinc Carbonate	X	X	X	X																	
Zinc Carbonate Hydroxide				X																	
Zinc Chloride	X	X	X	X	X			X					X	X		X	X				
Zinc Chloride Hydroxide		X																			
Zinc Citrate	X	X																		X	
Zinc Cysteinate																					
Zinc Gluconate	X		X													X					
Zinc Glutamate																					
Zinc Glycinate	X																				
Zinc Hexametaphosphate																					
Zinc Hydroxide	X																				
Zinc Lactate	X	X					X									X				X	
Zinc Laurate	X																X			X	
Zinc Myristate	X																X				
Zinc Neodecanoate																X					
Zinc Nitrate		X					X							X		X				X	
Zinc Palmitate																					
Zinc Phosphate	X						X													X	
Zinc Ricinoleate	X						X									X,O	O			X	
Zinc Salicylate	X	X																			
Zinc Stearate	X	X	X			X,O	X,O	X,O	O					X		X,O	O			O	
Zinc Sulfate	X	X	X		X	X		X		X			X	X		X	X			X	
Zinc Sulfide	X	X	X			X										X					
Zinc Undecylenate	X	X			X											X					

Note: ingredients that were previously reviewed are indicated in blue

ZINC SALTS SEARCH STRATEGY

Ingredient	Cas No.	Prev Rev	in Use	Info-base*	NTIS	FDA/ CFR	NTP	TOXNET	WHO	ECHA	EPA/ HPVIS	OECD/ SIDS	EU	NICNAS	Web
Zinc Acetate	**557-34-6; 5970-45-6**	Yes	Yes	X	-	X	-	X	-	X	-	-	X	X	X
Zinc Ascorbate	**134343-96-7; 151728-40-4**	No	Yes	X	-	X	-	X	-	-	-	-	X	-	X
Zinc Ascorbate Hydroxide	**No CAS #**	No	**	X	-	-	-	-	-	-	-	-	-	-	X
Zinc Aspartate	**36393-20-1**	No	Yes	X	-	X	-	X	-	-	X	-	X	-	X
Zinc Carbonate	**3486-35-9**	No	Yes	X	-	X	-	X	-	X	-	-	X	-	X
Zinc Carbonate Hydroxide	**150607-22-0**	No	No	X	-	-	-	-	-	-	-	-	-	-	X
Zinc Chloride	**7646-85-7**	No	Yes	X	X	X	-	X	X	X	-	-	X	X	X
Zinc Chloride Hydroxide	**12167-79-2; 55802-61-4**	No	No	X	-	-	-	-	-	-	-	-	X	-	X
Zinc Citrate	**546-46-3**	Yes	Yes	X	-	-	-	X	-	X	-	-	X	X	X
Zinc Cysteinate	**1197186-61-0**	No	No	X	-	-	-	X	-	-	-	-	-	-	X
Zinc Gluconate	**4468-02-4**	No	Yes	X	X	X	-	X	X	-	-	-	X	X	X
Zinc Glutamate	**1949-15-1**	No	No	X	-	-	-	X	-	-	X	-	X	-	X

ZINC SALTS SEARCH STRATEGY

Ingredient	Cas No.	Prev Rev	in Use	Info-base*	NTIS	FDA/ CFR	NTP	TOXNET	WHO	ECHA	EPA/ HPVIS	OECD/ SIDS	EU	NICNAS	Web
Zinc Glycinate	**14281-83-5**	No	Yes	X	-	-	-	X	-	-	-	-	X	X	X
Zinc Hexameta-phosphate	**13566-15-9**	No	No	X	-	-	-	X	-	-	-	-	-	-	X
Zinc Hydroxide	**20427-58-1**	No	Yes	X	-	X	-	X	-	X	-	-	-	-	X
Zinc Lactate	**16039-53-5; 554-05-2**	No	Yes	X	-	-	-	X	-	X	-	-	X	-	X
Zinc Laurate	**2452-01-9**	No	Yes	X	-	-	-	X	-	X	-	-	X	-	X
Zinc Myristate	**16260-27-8**	Yes	Yes	X	-	-	X	X	-	-	-	-	X	-	X
Zinc Neodecanoate	**27253-29-8**	No	No	X	-	-	-	X	-	X	-	-	X	-	X
Zinc Nitrate	**7779-88-6**	No	No	X	-	X	-	X	X	X	-	X	-	X	X
Zinc Palmitate	**4991-47-3**	No	No	X	-	X	-	X	X	-	-	-	-	-	X
Zinc Phosphate	**7543-51-3; 7779-90-0**	No	Yes	X	-	-	-	X	X	X	-	X	-	X	X
Zinc Ricinoleate	**13040-19-2**	Yes	Yes	X	-	-	-	X	-	X	-	-	X	-	X
Zinc Salicylate	**16283-36-6**	No	Yes	X	-	X	X	X	X	-	-	-	-	-	X
Zinc Stearate	**557-05-1**	Yes	Yes	X	X	X	-	X	-	X	-	X	X	X	X
Zinc Sulfate	**7446-19-7; 7446-20-0; 7733-02-0**	No	Yes	X	X	X	X	X	X	X	-	X	X	X	X

ZINC SALTS SEARCH STRATEGY

Ingredient	Cas No.	Prev Rev	in Use	Info-base*	NTIS	FDA/ CFR	NTP	TOXNET	WHO	ECHA	EPA/ HPVIS	OECD/ SIDS	EU	NICNAS	Web
Zinc Sulfide	**1314-98-3**	No	Yes	X	-	X	-	X	X	X	-	-	X	-	X
Zinc Undecylenate	**557-08-4**	No	Yes	X	-	X	-	X	-	-	-	-	X	-	X

X indicates data were available; - indicates no relevant data were available; *Online *International Cosmetic Ingredient Dictionary and Handbook*; **There are no reported uses for Zinc Ascorbate Hydroxide in the VCRP and concentration of use data from the Council Industry Survey are pending for this ingredient only

PubMed:

3-17-2017 Searched: ((("zinc acetate"[All Fields] OR 5970-45-6[All Fields]) OR "zinc ascorbate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ascorbate[All Fields] AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields]))) OR "zinc aspartate"[All Fields]) OR "zinc carbonate"[All Fields]) OR 3486-35-9[All Fields]) OR "zinc carbonate hydroxide"[All Fields]) OR "zinc chloride"[All Fields]) OR 7646-85-7[All Fields]) OR (("zinc chloride"[Supplementary Concept] OR "zinc chloride"[All Fields]) AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields]))) OR "zinc citrate"[All Fields]) OR "zinc cysteinate"[All Fields]) OR "zinc gluconate"[All Fields]) OR "zinc glutamate"[All Fields]) OR "zinc glycinate"[All Fields]) OR 14281-83-5[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("hexametaphosphate"[Supplementary Concept] OR "hexametaphosphate"[All Fields]))) OR "zinc hydroxide"[All Fields]) OR 20427-58-1[All Fields]) OR "zinc lactate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND laurate[All Fields])) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("myristic acid"[MeSH Terms] OR ("myristic"[All Fields] AND "acid"[All Fields]) OR "myristic acid"[All Fields] OR "myristate"[All Fields]))) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND neodecanoate[All Fields])) OR "zinc nitrate"[All Fields]) OR 7779-88-6[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND palmitate[All Fields])) OR "zinc phosphate"[All Fields]) OR 7543-51-3[All Fields]) OR "7779-90-0"[EC/RN Number]) OR "zinc ricinoleate"[All Fields]) OR "zinc salicylate"[All Fields]) OR "zinc stearate"[All Fields]) OR "zinc sulfate"[All Fields]) OR 7446-20-0[All Fields]) OR "zinc sulphate heptahydrate"[All Fields]) OR "7733-02-0"[EC/RN Number]) OR "zinc sulfide"[All Fields]) OR 1314-98-3[All Fields]) OR "zinc undecylenate"[All Fields]) NOT ("fishes"[MeSH Terms] OR "fishes"[All Fields] OR "fish"[All Fields])) NOT ecological[All Fields]) NOT ("nanoparticles"[MeSH Terms] OR "nanoparticles"[All Fields])) AND ("toxicity"[Subheading] OR "toxicity"[All Fields])Email alert for potential future articles matching the search terms above was setup (9-7-2016 and 9-8-2016).

There were 627 hits for the above search terms; 33 potentially useful hits.

3-17-2017 Searched: ((("zinc acetate"[All Fields] OR 5970-45-6[All Fields]) OR "zinc ascorbate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ascorbate[All Fields] AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields]))) OR "zinc aspartate"[All Fields]) OR "zinc carbonate"[All Fields]) OR 3486-35-9[All Fields]) OR "zinc carbonate hydroxide"[All Fields]) OR "zinc chloride"[All Fields]) OR 7646-85-7[All Fields]) OR (("zinc chloride"[Supplementary Concept] OR "zinc chloride"[All Fields]) AND

("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields])) OR "zinc citrate"[All Fields]) OR "zinc cysteinate"[All Fields]) OR "zinc gluconate"[All Fields]) OR "zinc glutamate"[All Fields]) OR "zinc glycinate"[All Fields]) OR 14281-83-5[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("hexametaphosphate"[Supplementary Concept] OR "hexametaphosphate"[All Fields])) OR "zinc hydroxide"[All Fields]) OR 20427-58-1[All Fields]) OR "zinc lactate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND laurate[All Fields])) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("myristic acid"[MeSH Terms] OR ("myristic"[All Fields] AND "acid"[All Fields]) OR "myristic acid"[All Fields] OR "myristate"[All Fields]))) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND neodecanoate[All Fields])) OR "zinc nitrate"[All Fields]) OR 7779-88-6[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND palmitate[All Fields])) OR "zinc phosphate"[All Fields]) OR 7543-51-3[All Fields]) OR "7779-90-0"[EC/RN Number]) OR "zinc ricinoleate"[All Fields]) OR "zinc salicylate"[All Fields]) OR "zinc stearate"[All Fields]) OR "zinc sulfate"[All Fields]) OR 7446-20-0[All Fields]) OR "zinc sulphate heptahydrate"[All Fields]) OR "7733-02-0"[EC/RN Number]) OR "zinc sulfide"[All Fields]) OR 1314-98-3[All Fields]) OR "zinc undecylenate"[All Fields]) NOT ("fishes"[MeSH Terms] OR "fishes"[All Fields] OR "fish"[All Fields])) NOT ecological[All Fields]) NOT ("nanoparticles"[MeSH Terms] OR "nanoparticles"[All Fields])) AND irritation[All Fields]

There were 19 hits from the above search terms; 3 potentially useful hits.

3-17-2017 Searched: ((((((((((((((((((((((((((((((((((("zinc acetate"[All Fields] OR 5970-45-6[All Fields]) OR "zinc ascorbate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ascorbate[All Fields] AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields]))) OR "zinc aspartate"[All Fields]) OR "zinc carbonate"[All Fields]) OR 3486-35-9[All Fields]) OR "zinc carbonate hydroxide"[All Fields]) OR "zinc chloride"[All Fields]) OR 7646-85-7[All Fields]) OR (("zinc chloride"[Supplementary Concept] OR "zinc chloride"[All Fields]) AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields])) OR "zinc citrate"[All Fields]) OR "zinc cysteinate"[All Fields]) OR "zinc gluconate"[All Fields]) OR "zinc glutamate"[All Fields]) OR "zinc glycinate"[All Fields]) OR 14281-83-5[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("hexametaphosphate"[Supplementary Concept] OR "hexametaphosphate"[All Fields])) OR "zinc hydroxide"[All Fields]) OR 20427-58-1[All Fields]) OR "zinc lactate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND laurate[All Fields])) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("myristic acid"[MeSH Terms] OR ("myristic"[All Fields] AND "acid"[All Fields]) OR "myristic acid"[All Fields] OR "myristate"[All Fields]))) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND neodecanoate[All Fields])) OR "zinc nitrate"[All Fields]) OR 7779-88-6[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND palmitate[All Fields])) OR "zinc phosphate"[All Fields]) OR 7543-51-3[All Fields]) OR "7779-90-0"[EC/RN Number]) OR "zinc ricinoleate"[All Fields]) OR "zinc salicylate"[All Fields]) OR "zinc stearate"[All Fields]) OR "zinc sulfate"[All Fields]) OR 7446-20-0[All Fields]) OR "zinc sulphate heptahydrate"[All Fields]) OR "7733-02-0"[EC/RN Number]) OR "zinc sulfide"[All Fields]) OR 1314-98-3[All Fields]) OR "zinc undecylenate"[All Fields]) NOT ("fishes"[MeSH Terms] OR "fishes"[All Fields] OR "fish"[All Fields])) NOT ecological[All Fields]) NOT ("nanoparticles"[MeSH Terms] OR "nanoparticles"[All Fields])) AND sensitization[All Fields]

There were 13 hits from the above search terms; 1 potentially useful hit.

3-17-2017 Searched: ((((((((((((((((((((((((((((((((((("zinc acetate"[All Fields] OR 5970-45-6[All Fields]) OR "zinc ascorbate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ascorbate[All Fields] AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields]))) OR "zinc aspartate"[All Fields]) OR "zinc carbonate"[All Fields]) OR 3486-35-9[All Fields]) OR "zinc carbonate hydroxide"[All Fields]) OR "zinc chloride"[All Fields]) OR 7646-85-7[All Fields]) OR (("zinc chloride"[Supplementary Concept] OR "zinc chloride"[All Fields]) AND

("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields])) OR "zinc citrate"[All Fields]) OR "zinc cysteinate"[All Fields]) OR "zinc gluconate"[All Fields]) OR "zinc glutamate"[All Fields]) OR "zinc glycinate"[All Fields]) OR 14281-83-5[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("hexametaphosphate"[Supplementary Concept] OR "hexametaphosphate"[All Fields])) OR "zinc hydroxide"[All Fields]) OR 20427-58-1[All Fields]) OR "zinc lactate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND laurate[All Fields])) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("myristic acid"[MeSH Terms] OR ("myristic"[All Fields] AND "acid"[All Fields]) OR "myristic acid"[All Fields] OR "myristate"[All Fields]))) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND neodecanoate[All Fields])) OR "zinc nitrate"[All Fields]) OR 7779-88-6[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND palmitate[All Fields])) OR "zinc phosphate"[All Fields]) OR 7543-51-3[All Fields]) OR "7779-90-0"[EC/RN Number]) OR "zinc ricinoleate"[All Fields]) OR "zinc salicylate"[All Fields]) OR "zinc stearate"[All Fields]) OR "zinc sulfate"[All Fields]) OR 7446-20-0[All Fields]) OR "zinc sulphate heptahydrate"[All Fields]) OR "7733-02-0"[EC/RN Number]) OR "zinc sulfide"[All Fields]) OR 1314-98-3[All Fields]) OR "zinc undecylenate"[All Fields]) NOT ("fishes"[MeSH Terms] OR "fishes"[All Fields] OR "fish"[All Fields])) NOT ecological[All Fields]) NOT ("nanoparticles"[MeSH Terms] OR "nanoparticles"[All Fields])) AND ("reproduction"[MeSH Terms] OR "reproduction"[All Fields])

There were 174 hits from the above search terms; 6 potentially useful hits.

3-17-2017 Searched: ((((((((((((((((((((((((((((((((((("zinc acetate"[All Fields] OR 5970-45-6[All Fields]) OR "zinc ascorbate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ascorbate[All Fields] AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields]))) OR "zinc aspartate"[All Fields]) OR "zinc carbonate"[All Fields]) OR 3486-35-9[All Fields]) OR "zinc carbonate hydroxide"[All Fields]) OR "zinc chloride"[All Fields]) OR 7646-85-7[All Fields]) OR (("zinc chloride"[Supplementary Concept] OR "zinc chloride"[All Fields]) AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields]))) OR "zinc citrate"[All Fields]) OR "zinc cysteinate"[All Fields]) OR "zinc gluconate"[All Fields]) OR "zinc glutamate"[All Fields]) OR "zinc glycinate"[All Fields]) OR 14281-83-5[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("hexametaphosphate"[Supplementary Concept] OR "hexametaphosphate"[All Fields])) OR "zinc hydroxide"[All Fields]) OR 20427-58-1[All Fields]) OR "zinc lactate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND laurate[All Fields])) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("myristic acid"[MeSH Terms] OR ("myristic"[All Fields] AND "acid"[All Fields]) OR "myristic acid"[All Fields] OR "myristate"[All Fields]))) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND neodecanoate[All Fields])) OR "zinc nitrate"[All Fields]) OR 7779-88-6[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND palmitate[All Fields])) OR "zinc phosphate"[All Fields]) OR 7543-51-3[All Fields]) OR "7779-90-0"[EC/RN Number]) OR "zinc ricinoleate"[All Fields]) OR "zinc salicylate"[All Fields]) OR "zinc stearate"[All Fields]) OR "zinc sulfate"[All Fields]) OR 7446-20-0[All Fields]) OR "zinc sulphate heptahydrate"[All Fields]) OR "7733-02-0"[EC/RN Number]) OR "zinc sulfide"[All Fields]) OR 1314-98-3[All Fields]) OR "zinc undecylenate"[All Fields]) NOT ("fishes"[MeSH Terms] OR "fishes"[All Fields] OR "fish"[All Fields])) NOT ecological[All Fields]) NOT ("nanoparticles"[MeSH Terms] OR "nanoparticles"[All Fields])) AND genotoxicity[All Fields]

There were 10 hits from the above search terms; 3 potentially useful hits.

3-17-2017 Searched: ((((((((((((((((((((((((((((((((((("zinc acetate"[All Fields] OR 5970-45-6[All Fields]) OR "zinc ascorbate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ascorbate[All Fields] AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields]))) OR "zinc aspartate"[All Fields]) OR "zinc carbonate"[All Fields]) OR 3486-35-9[All Fields]) OR "zinc carbonate hydroxide"[All Fields]) OR "zinc chloride"[All Fields]) OR 7646-85-7[All Fields]) OR (("zinc chloride"[Supplementary Concept] OR "zinc chloride"[All Fields]) AND

("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields])) OR "zinc citrate"[All Fields]) OR "zinc cysteinate"[All Fields]) OR "zinc gluconate"[All Fields]) OR "zinc glutamate"[All Fields]) OR "zinc glycinate"[All Fields]) OR 14281-83-5[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("hexametaphosphate"[Supplementary Concept] OR "hexametaphosphate"[All Fields])) OR "zinc hydroxide"[All Fields]) OR 20427-58-1[All Fields]) OR "zinc lactate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND laurate[All Fields])) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("myristic acid"[MeSH Terms] OR ("myristic"[All Fields] AND "acid"[All Fields]) OR "myristic acid"[All Fields] OR "myristate"[All Fields]))) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND neodecanoate[All Fields])) OR "zinc nitrate"[All Fields]) OR 7779-88-6[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND palmitate[All Fields])) OR "zinc phosphate"[All Fields]) OR 7543-51-3[All Fields]) OR "7779-90-0"[EC/RN Number]) OR "zinc ricinoleate"[All Fields]) OR "zinc salicylate"[All Fields]) OR "zinc stearate"[All Fields]) OR "zinc sulfate"[All Fields]) OR 7446-20-0[All Fields]) OR "zinc sulphate heptahydrate"[All Fields]) OR "7733-02-0"[EC/RN Number]) OR "zinc sulfide"[All Fields]) OR 1314-98-3[All Fields]) OR "zinc undecylenate"[All Fields]) NOT ("fishes"[MeSH Terms] OR "fishes"[All Fields] OR "fish"[All Fields])) NOT ecological[All Fields]) NOT ("nanoparticles"[MeSH Terms] OR "nanoparticles"[All Fields])) AND carcinogenicity[All Fields]

There were 7 hits from the above search terms; 2 potentially useful hits.

3-17-2017 Searched: ((((((((((((((((((((((((((((((((((("zinc acetate"[All Fields] OR 5970-45-6[All Fields]) OR "zinc ascorbate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ascorbate[All Fields] AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields])) OR "zinc aspartate"[All Fields]) OR "zinc carbonate"[All Fields]) OR 3486-35-9[All Fields]) OR "zinc carbonate hydroxide"[All Fields]) OR "zinc chloride"[All Fields]) OR 7646-85-7[All Fields]) OR (("zinc chloride"[Supplementary Concept] OR "zinc chloride"[All Fields]) AND ("hydroxide ion"[Supplementary Concept] OR "hydroxide ion"[All Fields] OR "hydroxide"[All Fields])) OR "zinc citrate"[All Fields]) OR "zinc cysteinate"[All Fields]) OR "zinc gluconate"[All Fields]) OR "zinc glutamate"[All Fields]) OR "zinc glycinate"[All Fields]) OR 14281-83-5[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("hexametaphosphate"[Supplementary Concept] OR "hexametaphosphate"[All Fields])) OR "zinc hydroxide"[All Fields]) OR 20427-58-1[All Fields]) OR "zinc lactate"[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND laurate[All Fields])) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("myristic acid"[MeSH Terms] OR ("myristic"[All Fields] AND "acid"[All Fields]) OR "myristic acid"[All Fields] OR "myristate"[All Fields]))) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND neodecanoate[All Fields])) OR "zinc nitrate"[All Fields]) OR 7779-88-6[All Fields]) OR (("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND palmitate[All Fields])) OR "zinc phosphate"[All Fields]) OR 7543-51-3[All Fields]) OR "7779-90-0"[EC/RN Number]) OR "zinc ricinoleate"[All Fields]) OR "zinc salicylate"[All Fields]) OR "zinc stearate"[All Fields]) OR "zinc sulfate"[All Fields]) OR 7446-20-0[All Fields]) OR "zinc sulphate heptahydrate"[All Fields]) OR "7733-02-0"[EC/RN Number]) OR "zinc sulfide"[All Fields]) OR 1314-98-3[All Fields]) OR "zinc undecylenate"[All Fields]) NOT ("fishes"[MeSH Terms] OR "fishes"[All Fields] OR "fish"[All Fields])) NOT ecological[All Fields]) NOT ("nanoparticles"[MeSH Terms] OR "nanoparticles"[All Fields])) AND ("pharmacokinetics"[Subheading] OR "pharmacokinetics"[All Fields] OR "toxicokinetics"[All Fields] OR "toxicokinetics"[MeSH Terms] OR "toxicokinetics"[All Fields] OR "pharmacokinetics"[MeSH Terms] OR "toxicokinetics"[All Fields])

There were 404 hits from the above search terms; 35 potentially useful hits.

Email alerts were set-up 3-17-2017 to receive updates on available articles corresponding to all of the above PubMed search terms.

SciFinder:

Searched Substance Identifier on 2-28-2017 for: Zinc Acetate; 557-34-6; 5970-45-6; Zinc Ascorbate; 134343-96-7; Zinc Ascorbate Hydroxide; Zinc Aspartate; 36393-20-1; Zinc Carbonate; 3486-35-9; Zinc Carbonate Hydroxide; Zinc Chloride; 7646-85-7; Zinc Chloride Hydroxide; 12167-79-2; Zinc Citrate; 546-46-3; Zinc Cysteinate; 1197186-61-0; Zinc Gluconate; 4468-02-4; Zinc Glutamate; 1949-15-1; Zinc Glycinate; 14281-83-5; Zinc Hexametaphosphate; 13566-15-9; Zinc Hydroxide; 20427-58-1; Zinc Lactate; 16039-53-5; 554-05-2; Zinc Laurate; 2452-01-9; Zinc Myristate; 16260-27-8; Zinc Neodecanoate; 27253-29-8; Zinc Nitrate; 7779-88-6; Zinc Palmitate; 4991-47-3; Zinc Phosphate; 7543-51-3; Zinc Ricinoleate; 13040-19-2; Zinc Salicylate; 16283-36-6; Zinc Stearate; 557-05-1; Zinc Sulfate; 7446-19-7; 7446-20-0; 7733-02-0; Zinc Sulfide; 1314-98-3; Zinc Undecylenate; 557-08-4

After duplicates were removed, the combined hits for the above search terms generated 1425 hits/ ~68 potentially useful hits.

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ZINC SALTS – TRANSCRIPTS

FULL PANEL – DEC 5, 2017

DR. BERGFELD: All right, we're through t eh final reports and some have come forward and some are going backwards, I guess. The next are reports advancing to the next level. And here is a group of new reports as well as some of the botanicals. Zinc salts. Dr. Marks?

DR. MARKS: So this is the first time the panel has reviewed these 28 zinc inorganic and organometallic salts. Our team felt that we can move forward with a tentative report safe for all 28 zinc ingredients as used in cosmetics. We have -- we will have some discussion points, but the motion is safe for all 28.

DR. BERGFELD: Belsito team?

DR. BELSITO: Yea. So we safe for 27. I twill let Dan comment on zinc sulfide.

DR. LIEBLER: Yea, I thought this was kind of almost a coin flip that in the course of our discussion yesterday I decided I would recommend that we should recommend we remove it. This is a molecule that unlike the others is almost completely insoluble. It doesn't dissociate readily into zinc and the counter ion. It parenthetically, also appears to have no uses. But I think that this chemically and sort of most likely you know, biologically doesn't belong in this group and so I thought I'd put t hat out for your consideration.

DR. BERGFELD: Ron Hill, you want to comment?

DR. HILL: I, by and large, concur with that. I had just made the comment that we get actual solubility data in here and then look at it. I think removing it is very logical based on chemical, lack of chemical similarity.

DR. BERGFELD: Jim, you want to amend?

DR. MARKS: Yes. So I will withdraw that motion and propose another motion that a tentative report be issued with a safe conclusion for all 27 zinc ingredients now removing the one, Dan, that you talked about.

DR. BERGFELD: The zinc sulfide? Is there a second to that?

DR. BELSITO: Second.

DR. BERGFELD: All right. Any further discussion regarding this I ingredient?

DR. MARKS: Yea, we felt there should be some things included in the discussion we will see in the next rendition that the draft tentative report. First of all, the zinc chloride is severely irritating at 1 percent and we have used data with a leave on 0.47 percent. So we were concerned that we don't know where the threshold for irritation is, but we should mention that in the discussion that it is severely irritating at 1 percent. And then also, we are concerned about the use of these zinc ingredients in mucous membrane, oral and lipstick products because the potential of ingestion. We wanted that dealt with in the discussion. And then lastly the inhalation boiler plate be put in.

DR. BERGFELD: Any comments form the Belsito team?

DR. BELSITO: Only if we want to discuss irritation should our conclusion be when formulated to be non-irritating.

DR. MARKS: We -- we -- yea, we discussed that yesterday. This seems to be a little bit different. All the other ones ingredients with data were non irritating. We thought about that. We decided to just do the safe and then mention the discussion the potential for irritation. Presumably, it's formulated to be non irritating, but we can put that in the conclusion if you think that is the safer way to go.

DR. BERGFELD: That's what we do.

DR. BELSITO: I think if you are going to discuss the potential for irritation the conclusion should state formulated to be non irritating.

DR. MARKS: Fine. Let's include that. I will again, withdraw my motion and propose another motion that's safe for all 27 ingredients when formulated to be non- irritating.

DR. BERGFELD: Is there a second?

DR. BELSITO: Second.

DR. BERGFELD: Ron Hill?

DR. HILL: Just to follow up on that zinc chloride we conjectured it looked like the irritation was coming from tests of just zinc chloride and water and then you'd have an acidic solution, relatively acidic solution and we felt like in formulation you would never see something comparable to that. But it doesn't mean that we don't have to put that in the conclusion.

DR. BERGFELD: Dan?

DR. LIEBLER: Well, I also suggested to Monice that we in the area of where it says natural occurrence on PDF 23 that we maybe expand that slightly to have a brief description of the natural physiology of zinc. It plays an important role in several important enzymes. It's a required nutrient, etc. And that needs to be captured in the report somehow.

DR. BERGFELD: Thank you. I think we can just end that. That's a good idea. Ron Hill?

DR. HILL: I think we also discussed -- we also discussed it in terms of observations that suggested some sort of genome effect that we conjectured that if you swap the system high enough that you are maybe messing with zinc fingers and the like. I don't remember what I asked for yesterday in terms of biology, but to make sure that we did capture that zinc biology in a way that could help with that.

DR. BELSITO: Paul? Do you want to?

DR. SNYDER: Just to comment it did say in the irritation section that in formulations that was tested it was non irritating. So it can be formulated to be non irritating.

DR. MARKS: And I think that's why we ended up with this safe conclusion and not including the non irritating but it's clearly I think to mention that in the conclusion.

DR. HILL: Yeah, we were puzzled that -- we noted that one and zinc sulfate are uniquely among these very soluble and we were puzzled why we didn't see the irritation with the sulfate. I think our discussion probably had a lot to do with exactly what was tested.

DR. BERGFELD: All right, any other comments before we move on to question? All those in favor of this conclusion please indicate by raising your hands. Thank you and I am saying that tone will be removed. That is the zinc sulfide. Is that correct?

[MOTION PASSED UNANIMOUSLY]

Belsito Team – Dec 4, 2017

DR. BELSITO: Safe as used, zinc salts, it's the first time. Five of the ingredients were previously reviewed and we're now looking at 23 more that include inorganic and organometallic zinc salts and the first question always is to Dan. Are we okay with this group?

DR. LIEBLER: Short answer, yes.

DR. BELSITO: In the table under zinc stearate and under a couple of others, there's an "X, O". What's the O stand for?

MS. FIUME: Old data.

DR. BELSITO: That needs to be --

DR. KLAASSEN: Footnote.

DR. BELSITO: I didn't see it footnoted. It needs to be footnoted. Well, I guess it doesn't, because that table is going to go away. I was just curious what it meant. Dan's okay with the grouping.

DR. LIEBLER: There may be a little pushback on zinc sulfide and -- because it's really dissimilar from the others and that it won't readily disassociate any aqueous solution to zinc and some counterion. It's very, very low solubility. It doesn't have any uses and barely any data, so I could compromise on that one. Then zinc neodecanoate, the neodecanoate part is double-ally branched fatty acid. I might anticipate an objection about that, but I honestly don't see any reason to be concerned about the neodecanoate part.

DR. BELSITO: So are you saying you would want to eliminate the zinc sulfide or see what the other team says?

DR. LIEBLER: See what the other team says.

DR. BELSITO: And the same with zinc neodecanoate?

DR. LIEBLER: Correct. As long as nobody in this room promises to tell, I'm prepared to compromise, David.

DR. KLAASSEN: In that regard, same compound that is used a lot is zinc pyridinethione, which is active ingredient in Head & Shoulders. Actually what happens with that is that the pyridinethione does go through the skin, but the zinc stays on the outside. I don't know if that is helpful or not.

DR. BELSITO: On page 21 of the PDF where it says about the numerous studies available in the open literature on the zinc salts, it says, that -- GRAS ingredients, the focus of our report is on data, other than oral toxicity bioavailability. Not all of the acids that are being combined with the zinc here necessarily are GRAS; right? I mean, neopentanoic acid is not GRAS.

MS. FIUME: I believe what this is saying is that for those GRAS ingredients (talk over), et cetera, for those ingredients, the ones that are GRAS, the focus is on the oral -- is not on the oral toxicity, the bioavailability of dermal and other, just for those GRAS ingredients that the focus won't be on the oral.

DR.KATZ: A quick question, GRAS for what?

MS. FIUME: When used with good manufacturing practices as nutrients for human consumption.

DR.KATZ: I'm confused, because GRAS -- are you talking GRAS for cosmetic ingredients, because there is no GRAS?

MS. FIUME: No, what we will attempt to do is if there is a large body of data and we know that an ingredient is deemed GRAS through the U.S. FDA for oral or food use, then that safety has been established and instead we focus on the topical uses of the ingredients. We're not calling it GRAS for cosmetics, we're just saying because it's a GRAS ingredient in food use, we're focusing on the derm on the topical --

DR.KATZ: You need to specify that that's actually what you're calling GRAS to avoid confusion as to what it is the term's meaning. I don't know if you say it that way in the report, but that's actually how it should be stated.

MS. FIUME: It does state specifically for nutrients as human consumption.

DR. BELSITO: But in looking at the data we have for the toxin points, there's the data on materials that you said you're not going to concentrate on. We don't have data on any of the other materials. I'm just saying do we need that data -- I mean, because it sounds like we're dismissing the need for tox data. Is this a report where we need to look and bring in -- obviously we're not worried about acetic acid or hydrochloric acid or any of these others, it's a report where we need to look at what else these are being combined with and have we reviewed their safety, because we really are dismissing --

SPEAKER: Everything on the list, the counterions for zinc, are common nutrient ingredients with a couple of exceptions, neodecanoate and the sulfide, zinc sulfide. Although H2S is in many -- sulfide is many things. It's in the body at some point or another, but you could maybe -- sulfate, resimilate, phosphate, metaphosphate, gluconic, glutamate, obviously all those --

DR. KLAASSEN: How about the last one (inaudible)?

DR. BELSITO: Well, we've already concluded neodecanoate.

DR. KLAASSEN: Okay.

DR. BELSITO: I was just saying the way it's worded, it's like we're dismissing all systemic toxicity, because these can be food additives and yet the systemic toxicity that we present is for the food additives without the ones that are not food additives. So in the discussion, I think something should be said about that.

DR. LIEBLER: Again it comes back to these two sort of oddballs that have no uses, but it's the neodecanoate and the sulfide. Those are the two where I don't know that you could clearly state that we need to review them before --

DR. BELSITO: We have neodecanoates that we reviewed.

MS. FIUME: We have done neodecanoates, I'm checking to see --

DR. LIEBLER: Really?

MS. FIUME: Well, in the larger report, we've done neodecanoates. Are you concerned specifically about the acid, whether the acid was reviewed?

DR. LIEBLER: Yeah, it's just the acid component. I sort of assumed that it had never been reviewed. I had never heard of it until I read this report and looked at the structure. If the panel has done those previously, then that one, my concern about that goes away.

DR. BELSITO: We have done other neodecanoates, that's not a (talk over) salt sulfides.

DR. LIEBLER: The sulfide, that's an inorganic molecule. There's nothing else exactly the same and read across like it, so that's the one that could still come out of this report. It's really dissimilar from the other --

DR. BELSITO: The sulfide.

DR. LIEBLER: Zinc sulfide, second to last one on the list.

DR. BELSITO: So you're suggesting that we delete it as not being an appropriate member?

DR. LIEBLER: Yeah.

DR. BELSITO: Does --

(Talk over)

SPEAKER: No, no recorded uses.

DR. BELSITO: Curt.

DR. LIEBLER: It's got no uses, but that's not a reason to delete an ingredient. It's the only one that's almost completely insoluble. It doesn't disassociate under aqueous conditions to zinc 2 plus and S minus, which would become H2S, so it just --

DR. BELSITO: We're deleting it from the report, because, unlike the other salts, it does not disassociate?

DR. LIEBLER: Right. It's insoluble, doesn't disassociate, doesn't behave like any of the others -- like all the others.

DR. BELSITO: Then safe as used? Dan, safe as used?

DR. LIEBLER: Yeah, nonirritating.

DR. BELSITO: Yes.

DR. LIEBLER: There's one other suggestion I had for the report. There was a note in Beth's memo about mentioning zinc and its binding the (inaudible) and I thought actually it would be good to have a brief couple three, four sentences, maybe a small paragraph, on zinc physiology pointing out that it's an essential nutrient, that it does have functions in certain enzymes, and that -- I don't know where we would put that. Could it be combined with natural occurrence? In natural occurrence you start to go down that road in the first paragraph. It's right before use. It's on PDF 23, but then you talk about its presence in various mineral materials.

MS. FIUME: I will find a good place for it. I will start looking -- I will look there, see if that works there and I will put it somewhere.

DR. LIEBLER: Yeah, it's obvious. I think it would be a good idea to have a little bit on zinc physiology, because this is in a central nutrient and that needs to be acknowledged.

DR. KLAASSEN: Physiological functions.

DR. LIEBLER: Right.

DR. SNYDER: So I just have one final comment. I wonder if the Reach dossier was funded by Republican or the Democratic party.

DR. BELSITO: Reach is European.

DR. SNYDER: I'm just joking.

DR. BELSITO: So in the discussion, heavy metals obviously, impurities, right, the respiratory boilerplate is used in aerosols.

DR. SNYDER: Heavy metals.

DR. BELSITO: I already said that. Are you concerned about the DART studies? Do we mention that in the discussion giving the levels of use or do we not bring that out? The DART studies are 26 in the PDF.

DR. SNYDER: I didn't have it tagged, so --

DR. BELSITO: So we just -- they're very high levels, so we got rid of those. Do we discuss the variable Genotox data or do we given the negative carcinogenicity dismiss that? I'm sorry, positive carcinogenicity at a very high dose level.

MR. ZIMMERMANN: On heavy metals, what's the limit?

DR. BELSITO: The standard limits. We have a boilerplate. I don't know, look at the boilerplate.

MR. ZIMMERMANN: There's no place in the world where zinc ore exists without lead.

SPEAKER: Well, it says cadmium and --

MR. ZIMMERMANN: Yeah, there are others, but zinc especially and lead are always found together. When you use zinc for industrial purposes, such as zinc stearate for vulcanizing rubber, they don't care about the lead, but we do. So I'm concerned about the lead content and the zinc.

DR. BELSITO: We have a standard boilerplate for heavy metal contamination, that's the one we use. What's the level for that, one --

MR. ZIMMERMANN: 10 PPM for zinc salts I think is too high, because we need refined zinc for what you're using it for or what we're using it for in cosmetics as opposed to -- zinc ores, zinc -- which hasn't had the total lead removed from it.

DR. BELSITO: I'm not following you, David.

MR. ZIMMERMANN: The way ores exist, they're mixtures. Now, you can take (talk over) -- you can take this zinc and depending on how you refine it, you can remove all the lead, which is what we use for zinc oxide for drug use and for the zinc salts, which are used in foods and things like that, or you can use the cheaper grade, which still has higher parts per

million than we're limited for industrial use. That's exactly what we don't want. I don't want to see industrial zinc stearate used as a cosmetic ingredient --

DR. ANSELL: The council has recommendations for lead in finished goods. FDA has endorsed lead levels.

MR. ZIMMERMANN: This is one of the major sources of lead that can exist.

DR. ANSELL: Right. I don't think we got to how it got in there, but the finished goods should be controlled to assure select raw materials that would not result in lead levels exceeding at least our recommendations.

MR. ZIMMERMANN: I'm just concerned about it, because that's the one that whenever I find higher levels of lead with a couple of exceptions, it's always traced back to the zinc.

DR. ANSELL: I think the current boilerplate is sufficient for that (inaudible).

DR. BELSITO: So to continue, there were some hepatomas, malignant lymphomas noted in a carcinogenicity study, but at very high doses. So do we think that the Genotox studies covered that, do we need to bring it into the discussion at all?

DR. SNYDER: No, I didn't --

DR. KLAASSEN: We did have some positive --

DR. BELSITO: Right.

DR. KLAASSEN: There were many, many tests. I think it probably needs to be discussed.

MS. FIUME: They were not higher in treated animals compared to --

DR. SNYDER: Yes, she used a double negative. It should just be no differences (inaudible) --

DR. BELSITO: Did I misread the carcinogenic study?

DR. SNYDER: Yeah. The first time I read it, I thought it's positive. Then I re-read it and it was like no.

DR. BELSITO: So then we don't need to worry about that. On page 28 of the PDF in the discussion, do we want to talk about the high concentrations that are used around the eyelashes and eyebrows in terms of this depigmentation? This is page 28 of the PDF where it says that there was -- hair shaft depigmentation was observed during multiple hair cycles and treated animals. Since it's used in high concentration in eyelash, eyebrow that it should not be formulated to cause depigmentation.

DR. SNYDER: I read through that a couple times. The mice had to go through several hair cycles. It went from a black to a brown pigment. It wasn't really like a true depigmentation, so I didn't really know what to do with that study to be honest.

DR. BELSITO: I don't know what to do with it either, but it's used in very high concentrations in eye products. If it not depigment, but if it changes the pigment of the eyelash or eyebrows that would not be a cosmetic function, right, because it changes the structure and/or function? I'm just pointing it out.

DR. SNYDER: To be honest, I didn't know what to do with it, because it's --

DR. BELSITO: The question is: Do we bring it into the discussion that it should not result in any pigment alterations of the eyelashes or eyebrows?

DR. ANSELL: But you notice the dose was 1.2 grams --

DR. BELSITO: I understand, that's what I'm saying. The comment used, since it was used in very high concentrations in these studies, it is used in high concentrations about the eyes as well right, what's the --

DR. ANSELL: But not at one-and-a-half grams per kilo.

DR. BELSITO: No, I understand, that's what I'm saying. You bring it into the discussion and say safe as used and you point out that although it's used in high concentrations in eye products, it's not used at this concentration.

DR. BERGFELD: I've never seen that (inaudible), have you?

DR. BELSITO: No, it's not going to happen. What I'm saying is we have this data here and I was just pointing out do we need to put it in the discussion and say we're not concerned about it, because even though it's used in high concentrations in eye products, it was used in exorbitantly high concentrations in these animal studies?

DR. SNYDER: Just put it in like that, just one sentence.

DR. BERGFELD: Are you going to use the word exorbitant?

DR. BELSITO: No, no, we'll use the actual doses. So formulated to be nonirritating is in the discussion, given the irritation data. The LLNAs were negative. So really safe as used when formulated to be nonirritating, the heavy metal boilerplate discussion about the changes in hair pigment, respiratory boilerplate, and that's it. Anything else? Okay.

DR. MARKS: I think so. We have a draft report here so that means this is the first time we've seen these 28 inorganic and organometallic zinc salts; although, we have reviewed a couple in the past: zinc acetate, zinc citrate, zinc myristate, zinc ricinoleate, and zinc stearate. And actually most of these were included in reports with a similar group of compounds so there may not be a lot of individual data in those reports on those zinc compounds, but because the group was safe we concluded those were safe. So I think the first thing we need to do is look at these 28 compounds and say do we like them and should any be eliminated from evaluation in this report. And that's the table - - I'm looking at this table here which starts with zinc acetate and then finishes with zinc undecylenate and that's the one in which there's the scoreboard of what tox data we have. Any of those ingredients be eliminated, Ron, Ron, Tom or are they all okay?

DR. SHANK: I didn't - -

DR. MARKS: Okay. Good.

DR. HILL: I didn't either but I do have another sort of an operational question. We've got at least two that are drug substances so (inaudible) can be sold as an OTC drug so how do we deal - - I know we've dealt with the undecylenate before which is an anti-fungal. How do we deal the fact that they're in cosmetics? Do we still vote to review them in their cosmetic uses and - -

MS. FIUME: Yes, we reviewed them in their cosmetic uses and concentrations.

DR. MARKS: Yes, you'll remember some of the ingredients in the past. Most of the data was actually from studies of medicinal purposes of the ingredients.

DR. HILL: So there's a philosophical thing here which is that we tend to pretty much ignore pharmacology even when it exists for something that has drug-like activity in our reports and I'm not sure that that feels entirely appropriate, and so I don't know how we think about when we run into that situation, when we know there's specific biological activity. Although, nobody knows how salicylates work quite frankly. We have - - after only two years we really don't know.

DR. SHANK: We don't ignore the pharmacological - -

DR. HILL: I didn't say ignore. Did I say ignore?

DR. SHANK: You said ignore.

DR. HILL: Okay, I apologize for that choice of words.

DR. SHANK: We certainly take that into consideration.

DR. MARKS: And I hate to bring up again, but some of these ingredients are GRAS, so I don't know if we're going to get into the discussion of what GRAS is or not, but any rate.

DR. SHANK: Absolutely. That it is.

DR. MARKS: Ron, Ron, and Tom what needs do you have to move forward in this? I actually have an insufficient data announcement because I'd like to see some sensitization and irritation data, but what else do we need?

DR. HILL: I wrote something vague and maybe Dr. Shank can further comment. I wrote there are a number of toxicities that appear in the report and they're discussed. And I feel like, in some cases, we don't have a good set of exposure estimates for the ingredients in relationship to some of those end points. It's a vague statement but - -

DR. SLAGA: The one potential data need would be genotoxicity with (inaudible) and maybe it would be worthwhile to have a few more just to have - - to pick out whatever the trend is, but - -

DR. HILL: That's what I was looking for is a kind of a dose response because I think if you swap out systems with zinc you're probably beginning to mess with things like zinc fingers and so forth, but I doubt that it's relevant but without having a sort of a clearer sense of what those dose responses are, it's hard to draw firm conclusions.

DR. MARKS: And more genotoxicity - - I'll give you what I had on the sensitization data. So interestingly zinc stearate was already in a previous report but at a group of - - let me see here. I have stearate, yes. So that's used at

percent. There's a lot of uses, over 2000 uses. And we don't have any sensitization data of that use so I'd like to have 32 percent sensitization data whether it be local lymph node, HRIPT, or guinea pig max. And then zinc myristate at 20 percent, we have 59 uses. Twenty percent is the highest concentration on (inaudible) so I'd like to see some sensitization data on that. On the zinc acetate which we do have irritation and sensitization data, that looked okay from the previous reports, but the other zinc compounds that were deemed to be safe, we have no irritation or sensitization data other than zinc chloride is a (inaudible) at one percent and we have no data on irritation and 0.47 percent which is the leave on concentration so I'd like to see irritation data on that. We have two compounds - - sensitization data and one with irritation data, and I don't know

whether you all had other compounds you wanted to see or ingredients. Those are the ones I kind of picked out since we're going to do an IDA.

DR. HILL: I wasn't concerned about sensitization in such cases because these are simple salts. I mean, zinc - - as soon as you put zinc myristate in solution the myristate's going that way, the zinc is going that way so really we're looking at sensitization to myristic acid or myristate conjugate, the conjugate base of that and I don't - -

DR. MARKS: So you aren't concerned?

DR. HILL: No, I don't have that - -

DR. MARKS: And the same with the stearate then?

DR. HILL: No, the irritation questions are valid wherever you feel like there's missing data but no, I don't think any of those are - - when you look at stearate, I don't think there's going to be any difference between that and sodium stearate. Would anybody have any other opinions in terms of chemistry? These are just fully dissociable salts; they're not organozinc compounds. Organozinc implies that the bond between the zinc and the carbomer, perhaps the zinc and phosphorous or sulfur or something so they're not - - they're just salts; zinc salts.

DR. MARKS: Yeah.

DR. HILL: So if you don't see sensitization to sodium myristate, there's no reason to believe you would see it to zinc myristate. Now - -

DR. MARKS: Nickel is in salts, right? And nickel is a big sensitizer and I think - -

DR. HILL: Yeah, because it's nickel.

DR. MARKS: Yeah, I agree. Zinc, clinically has not been an issue. But it'd be nice to have, other than the one, the zinc acetate, have some data. But I agree with you, Ron. I think the chances are little but would the insufficient data announcement, I think take that into consideration or should we just say we don't need it?

DR. HILL: I don't need it.

DR. SHANK: Well then can you read across for everything? The only thing you're considering is zinc itself.

DR. MARKS: Yeah.

DR. SHANK: So whatever data we have, some of these salts we can read across - -

DR. HILL: I suppose irritation was - - that's a question mark for some of them. But I would think, for example, if you don't see it with zinc borate you're not going to see it with zinc neodecanoate or myristate or any of these chain fatty acid ones, palmitate; I don't have any reason to think that they'd be any different.

DR. MARKS: We don't have a lot of sensitization. Basically zinc ricinoleate, 5 percent was okay. Zinc stearate, 10 percent was okay. Zinc sulfate, 10 percent was okay. So maybe you're right, Ron. These were higher concentrations; 32 percent and 20 percent, but if they aren't sensitizing at that - - and your simple salt - -

DR. HILL: It was interesting - -

DR. MARKS: Ron Shank, what do you feel about that?

DR. SLAGA: Safe.

DR. SHANK: Well it depends on how you look. If all you're worried about is the zinc ion then you can collectively put all these different salts together and then they'll probably safe as used.

DR. SLAGA: I mean, that's where we're gone. We really don't need the genotoxicity, but if it's the first time - -

DR. MARKS: I hear you. Well maybe we'll say we don't and we don't need the sensitization data. Do we feel comfortable with zinc chloride at 1 percent as a severiorde and the leave-on is 0.47 percent then. I didn't seek data - -

DR. SHANK: Zinc chloride seems to not fit. Zinc chloride is highly irritating at 1 percent. But zinc sulfate isn't at 50 percent. I don't like using read across for all of them.

DR. MARKS: Right.

DR. HILL: It is odd that if you see something with zinc chloride, why don't you see it with zinc sulfate. I can't come up with a good explanation. I was about to say the zinc chloride is a lot more soluble than many of the other ones but sulfate's surely more soluble than the chloride. I think; maybe not. We don't have water solubility on some of these, and that was something I only asked about with this sulfide which is seems to be used in fluorescent Halloween makeup. But it's not listed as a function.

DR. EISENMANN: Because that's a colorant and that's not one of purview. That's FDA's. And it's - -

DR. HILL: The fluorescent colorant?

DR. EISENMANN: Right, the fluorescent colorant is - - and it's got additional copper something in it.

DR. HILL: There's copper in there to cause the fluorescents to occur, okay. But the FDA's on that one so we don't consider that.

MR. DEWAN: Let's go to the petition process please.

DR. HILL: Yeah, because they limit the use of that too.

MR. DEWAN: Yes, yes.

DR. EISENMANN: I got a comment from a member on Friday. They would like to see the concentration of use information also be presented by zinc. Would you find that useful? They especially were concerned with this for the oral care issues in other jurisdictions they limit it by amount of zinc. So that was my question; would you like the information in the concentration of use table also to be presented by zinc in addition to the compound.

DR. HILL: You know, it's interesting because the place I flagged that was actually on the genotoxicity in the sense that we've got all these things presented in microgram per mil or microgram per liter and dose response goes by micromolar and nanomolar and millimolar. I know it's hard to convince people that weight per milliliter doesn't matter - - or you need to do the calculation, but anyway I actually scribbled a couple of those so yes that's a short answer to that question.

DR. MARKS: Yes, you would like it.

DR. HILL: Yes.

DR. MARKS: Then are you doing a margin of say - - how does the oral relate - - you're going to want for each one of these if you don't have it on a particular compound? I mean, how are they going to - -

DR. HILL: I don't think so because if it's the amount of zinc - - I mean, I asked the question. I sat and asked the question for quite awhile, would any of these more exotic counterions allow for ion pairs of zinc to be more self-(inaudible), for example, but - - or more skin penetrable but I don't think so. I've never seen anything to that effect over all the years of looking at things like zinc salts.

DR. MARKS: Ron Shank, do you need that?

DR. HILL: But if you remember how I started the discussion before he - -

DR. SHANK: The concentration of zinc in each of these salts.

DR. EISENMANN: So the concentration of use table would have like a column of - - what's the concentration as reported to me is (inaudible) and then you'd normalize it to how much zinc. And zinc is - -

DR. HILL: Percentage by weight of zinc.

DR. EISENMANN: Right.

DR. SHANK: I understand that, but the formulation is always by percentage of the ingredient, not - -

DR. EISENMANN: Except that in some jurisdictions, the amount in oral care products is regulated by the amount of zinc, and that's in here in the, I think, cosmetic use section. So that somebody can actually see what concentration of zinc, so especially - - they were especially concerned with the oral care area; maybe just that area that they wanted to see so you can see if they're corresponding to what's the regulations in other jurisdictions.

DR. HILL: And there's a basis for that which I think is - -

DR. SHANK: I don't know - - I don't object to having that information.

DR. MARKS: I wouldn't put it in if we aren't going to use it. I think it can be confusing and confounding. Then they'll spend a lot of time discussing and - -

DR. HILL: Well no, because for those responses that for many of these end points, and that's what I was driving at in my first comment, is based on how much zinc is there then the percentage of zinc tells you a lot.

DR. SHANK: Okay. For the organic zinc ingredients, is the zinc completely dissociated?

DR. HILL: Yeah. Now again, how fast that happens is going to depend on the water solubility, but that's about it as far as I know.

DR. MARKS: There are mucous membrane products, zinc aspirator's used and it's zinc chloride interestingly is also despite how irritating it is. And mucous membrane refers to oral/genital, is that right; or just oral?

DR. HILL: Or nasal if there's any - -

DR. MARKS: Or nasal, yeah. Do you know Carol?

DR. EISENMANN: In this case I think it's mostly oral because it is used in oral care products.

DR. MARKS: And here's one with - - so they're definitely oral use. Well if we want that data - - well we could still get that even if we issue a tentative report. I get the sense my team's thinking - -

DR. SHANK: Four of these are GRAS and can be used in (inaudible).

DR. MARKS: Yes.

DR. EISENMANN: Well zinc is essential - -

DR. SHANK: That can be a smaller exposure than the cosmetic use. And if it's only the zinc you're worried about, then why aren't all the others GRASable? We've got a new word.

DR. MARKS: I like that.

DR. HILL: Actually I think there's a pretty large range that are, but then some of them are for secondary use like packaging components or washes or that sort of thing, but I don't - -

DR. MARKS: No, I think your point is well taken. They have risks and you're concerned about zinc. Why would you - - you can read across with that. The rest should be fine.

DR. SHANK: I agree with that except for zinc chloride.

DR. MARKS: Zinc chloride and that's the - -

DR. SHANK: That's the stinker.

DR. HILL: But only irritation, right?

DR. SHANK: That's important.

DR. HILL: It is important. It is important.

DR. SHANK: It doesn't compare with the (inaudible) the way the others did.

DR. HILL: I wonder, really, how solid that information but the big thing I could say is that that one and that one alone other than the sulfate are very water soluble, and a lot of these are quite insoluble and I don't think our physical, chemical data table has those solubilities, but I think I'm stomping for that in my comments here.

MS. FIUME: So it often says that it's soluble or insoluble. Zinc sulfide says insoluble in water.

DR. HILL: Well and I wanted a number. I think that number's available and I asked for that in here, because I think you can use that really extreme insolubility in that case to support lack of concern; I forget which end point I put, but I've got it here.

DR. MARKS: So let's go back to Carol's comment. Do we need a zinc concentration on all these relevant to this - - is it a regulation on oral exposure or - -

DR. EISENMANN: I think there's a preliminary opinion right now from SCCS, and it hasn't gotten final yet.

DR. BJERKE: I think if you look at zinc, I think the route and administration are very important. I think the zinc does not get across the skin in a great extent, but for oral administration, zinc acetate, zinc gluconate they're used as dietary supplements. So I think that's what the concern is. You don't want to exceed the allowable daily intake limit and with zinc being orally absorbed it really is dependent on whether the individual is sufficient, deficient, or has excess zinc, because the body will kind of self-calibrate how much the absorption is. So I think if you're going to look at zinc content, I would maybe consider that for only those that have oral ingestion which would be like the (inaudible) for oral exposure.

DR. HILL: Yes, point well taken. It would only have to be the ones where there's oral exposure.

DR. MARKS: That's where I went on the mucous membrane, not all of them have them have mucous membrane products, but then again you've got to say I guess - - is there enough zinc in a cosmetic product unless you drink a whole bottle of it.

DR. HILL: That's what I was going to say. I don't think the mucous membrane exposure is the issue. I think instead of getting systemic viability and that's where I was looking for this sort of better information about some of these thresholds but beyond that I don't think we're anywhere close on any of these. I think my gut feeling is we're safe on all of these.

DR. MARKS: Let's go back to Carol. So it sounds like we don't need to have a separate column of the concentration - -

DR. HILL: I think we should on the ones that are used orally.

DR. EISENMANN: On the oral care products.

DR. HILL: Like mouthwashes, toothpaste.

DR. EISENMANN: On the oral care products, not the other ones.

MS. FIUME: But then aren't you giving the impression that you're expecting that these people aren't using it as expected, we're actually swallowing and ingesting a large amount of the product which isn't what we would normally expect in a mouthwash or a toothpaste. That's why we use incidental and not ingested.

DR. HILL: But that's the whole point, is that we're showing that the exposure is way below that and no problem, but at least you're working with the right substance which is the zinc.

MS. FIUME: But are we better off doing that just as a paragraph in the discussion rather than introducing an entire oral toxicity and ingestion about zinc?

DR. MARKS: Personally I like that you could get what the range is, and then say that the amount of exposure from mucous membrane products containing these zinc compounds - - I think exposure to zinc is insignificant from a toxicological point of view.

DR. HILL: It's not the mucous membrane, it's the swallowing mouthwash. It's the swallowing of toothpaste.

DR. MARKS: Yeah. So then you get into - -

DR. HILL: I think we have to get into there because of it being used in mouthwashes and toothpastes. It's that we do talk about consumers using things the way they're made.

DR. MARKS: I hear you. So what I'm saying is do you put the - - we're going to have to have a paragraph in the discussion no matter what.

DR. HILL: How many ingredients - -

DR. SLAGA: Which are the ones that we used for - -

DR. HILL: Is it just three or four?

DR. SLAGA: Zinc citrate.

MS. FIUME: So orally or as dentifrices in mouthwashes?

DR. MARKS: It says mucous membranes so I assume - -

MS. FIUME: So the incidental ingestion, with lipstick it could be incidental ingestion, the dentifrices. That's what goes into - - when you see incidental ingestion most of the time in our reports, it's going to be from a lipstick.

DR. HILL: So we need to break that out into - - of course most toothpastes are OTC drugs because they got fluoride anyway. So it's really mouthwashes that don't have - -

DR. EISENMANN: I think I did get some other oral care products so I'd have to look at the original table and - -

MS. FIUME: So then PDF page 78 is the VCRP data that we have. So zinc acetate is used in mouthwashes and breath fresheners.

DR. HILL: Page 78, you said?

MS. FIUME: Yeah, PDF page 78.

DR. MARKS: That's different than - -

MS. FIUME: Zinc chloride is used in dentifrices and mouthwashes and breath fresheners and other oral hygiene products. Zinc citrate is used in dentifrices - -

DR. SHANK: Lactate.

MS. FIUME: Yes, lactate.

DR. HILL: I don't know how worrisome - - I think dentifrices are potentially significant additive route of exposure so I'm thinking any of the ones that say dentifrices - - we don't break out mouthwashes here anywhere do we? Oh yeah we do; mouthwashes, breath fresheners, other oral hygiene products, all those three. And what all ingredients are used? I was getting at - - if it's four ingredients, if it's the gluconate, the chloride, the acetate, the citrate and that's all, we could easily deal with it with a paragraph. But if there's ten of them I think we should put zinc percentage separately on the tables.

DR. MARKS: Well you could give a range with a paragraph.

DR. HILL: We could.

DR. MARKS: And I think we have to have a paragraph anyway now because if you highlight it in a table they're going to say why did you put the amount of zinc individually in there.

DR. HILL: Because the toxicological endpoints that we're worried about, if you exceed them - -

DR. MARKS: Yeah, I know, but I think - -

DR. HILL: Ingestion - -

DR. MARKS: I think you'd have to have a paragraph in the discussion, Ron, no matter what.

DR. SLAGA: Discussion, somewhere - -

DR. HILL: I agree. I'm not saying you shouldn't. But I'm saying you're saying that's sufficient and I'm saying that I would like to see if we've got six or eight ingredients I don't think it's going to be hard to calculate percentage zinc because you've got the formula weights, and put them as well.

DR. MARKS: Yeah, we agree. It's just how do you display it. Do you display it in a table or do you display it as a range in a paragraph.

DR. HILL: Without seeing the data I don't know.

DR. MARKS: Well Monice, we'll let you and Carol decide which one and then you'll be showing it to us again in the next rendition of this report, because we also have to put it in perspective of what - -

MR. DEWAN: Exposure and how much - -

DR. MARKS: What's the maximum recommended in oral ingestion and so that we come anywhere close to that from a cosmetic exposure. Now, you're right, if there's a lot in a dentifrice instead of spitting out the dentifrice you ingest it, you're going to get a lot more exposure. It sounds like we're getting closer to IDA, an insufficient data announcement rather than a tentative report, but I don't know.

DR. HILL: That's not really a data need though, that's just a calculation for us to do.

DR. MARKS: Okay.

DR. HILL: And a way of displaying the data so I don't think that holds anything up, in my opinion.

DR. SLAGA: They're not giving data - -

DR. MARKS: That's true. You don't really need more genotoxicity data.

DR. SLAGA: My initial one was like Ron. I think it's safe based on (inaudible) the past ones that we reviewed and were safe.

DR. MARKS: Yeah, as I said the past ones we reviewed, it wasn't the zinc so much that was driving it, it was the group of compounds that zinc was attached to. How do we deal - - to my mind it, the only thing is - - it sounds like we're fine with sensitization. What do we do with the irritation of zinc chloride? Do we have a tentative report and put a either an insufficient for zinc chloride or do we do formulate to be non-irritating? Because that way you could get away with, get around an insufficient data.

DR. SLAGA: We really don't have a problem with the other ones, do we?

DR. MARKS: No.

DR. SLAGA: So to formulate it to be non-irritating for one compound - -

DR. SHANK: Do we know how solid that information is on zinc, severity or getting it - - It is a GRAS - -

DR. SLAGA: It is a GRAS.

DR. MARKS: I think there were several studies that - - it wasn't just one. Let me take a look here.

MS. FIUME: It was irritating in rabbit and mouse and guinea pig. In the table on page 61 of the PDF it shows that it's either irritating or severely irritating on three species. Now the source is a published document, Interspecies Variations in Response to Topical Applications of Selected Zinc Compounds is the title of the reference and it was published in Food Chem Toxicol.

DR. SHANK: Okay.

DR. EISENMANN: But they do give the pH of zinc chloride at 1 percent as 5.6.

DR. HILL: And I think that's the source of the irritation.

DR. SHANK: Do we have to rethink (inaudible).

DR. HILL: Probably not. My guess is that if they had buffered it, it wouldn't be irritating unless they buffered the pH 4.

MS. FIUME: Because there are other studies that report irritation, reference 8 is - - it came from the ECHA dossier as well.

DR. SHANK: Okay, well - -

DR. HILL: That's why I was asking for a threshold. Do they have a threshold where both certain - - I'm working on finding it.

DR. MARKS: No, that's why I was concerned, because it's being used at 0.47 percent, and we know 1 percent is severely irritating based on this data we have so what is the non-irritating concentration? It would have been nice to know they had something around there saying it was non-irritating at say 0.5 percent.

DR. EISENMANN: The concentration will be the only thing that will determine whether or not it's irritating.

DR. MARKS: Yeah, pH as you mentioned.

DR. SHANK: Is it irritating in formulation? You know, if it takes tests just soft. It's not necessarily fair. You test it in formulation.

DR. MARKS: Can we handle that in the discussion?

DR. SHANK: Well if we say formulating - -

DR. MARKS: No, I'm saying that would be the conclusion. We just have a safe conclusion and then point out in the discussion that zinc potentially can be irritating.

DR. SHANK: Yes, do it that way.

MS. FIUME: So only in the discussion?

DR. MARKS: Yes, that's - - well I suggest that as another alternative since the - -

DR. SHANK: I think that'll work.

DR. MARKS: Ron Hill?

DR. HILL: Yeah, I would be fine with it.

DR. SLAGA: I'd be fine with it too.

DR. MARKS: Okay. So it looks like tomorrow I'll move that we issue a tentative report with a safe conclusion for all of these, ingredients, zinc ingredients, these 28 zinc agreements.

DR. HILL: I again have an interesting - - and this is probably been editorial but on page 22 in the discussion of zinc carbonate they were talking about impurities and all we have is minor, and I thought I would like to see more clarification of minor because if it's cadmium of a significant percentage, that would be very different than - - but then I said I'd be okay with specification data from product data sheets so I don't know - - But if we have our heavy metal boilerplates, I think that covers it. Doesn't it, really? I mean, cadmium is certainly a magic one. That'd be one I'd be more worried about than others because it mentions it specifically.

DR. MARKS: Tom, do you want to make any mention of the genotoxicity or not? No, okay. So I think what we'll - - so again, the bottom line is safe for all 28 of these zinc ingredients. The sensitization data, if it comes up - - I don't know that we'll need to use it or mention it that 32 percent of the zinc stearate and zinc myristate is 20 percent. I think we can just - - we've already said we can read across. That's okay. The irritation data we're going to handle in the discussion and the concentration of zinc in mucous membrane oral lipstick products, we're going to deal with in the discussion.

DR. SLAGA: Sounds good.

DR. MARKS: And so we'll see that at the next draft final report.

MS. FIUME: And so for - - also for discussion the normal inhalation caveat will be fine for these ingredients as well, because we're using (inaudible).

DR. HILL: Yes. The other comment I had about the genotoxicity thing is because I think it is concentration of zinc and there's a lot of information. If we could find something mechanistic - - I mean, I probably should have done this search but time wise - - something to indicate, because obviously if you get enough zinc there, there is some genotoxicity going on, roughly what the mechanisms are and do we have any idea about thresholds. Ideally on mammals, not cells.

MS. FIUME: Carol, do you want to discuss that other item that you had in the comments or - -

DR. EISENMANN: No.

DR. HILL: A comment that we got, or - -

DR. EISENMANN: No, I - -

DR. HILL: That's okay. It's not one I haven't supposedly seen.

DR. EISENMANN: I wrote down a comment and they can consider it.

DR. MARKS: Okay, any other comments about the zinc salts? If not, we'll move on.

MS. FIUME: Dr. Marks, can I ask one more question to be safe.

DR. MARKS: Sure, of course.

MS. FIUME: I don't think, I don't see it in this report currently - - I don't have information from the previous reports, the stearate myristate reports. Would you like that information in for the supporting information if we're going to read across to the base acid because of dissociation? Does that question make sense?

DR. HILL: You're talking about where you tabulate we have these formal reports looking at these? I know it's a lot of work.

DR. MARKS: I don't know that you have to put the whole thing in. I actually went back to read them because I wanted to see what kind of irritation and sensitization data they had.

DR. SLAGA: Could we add summary in it?

DR. MARKS: Yeah, that's what I'm thinking, a summary in your report.

DR. SLAGA: You have done that before, just put the summaries.

MS. FIUME: We've done the summaries in italics and we've also tabulated the information from the reports, and I can do it whichever way is more helpful to the panel. And if you want it, do you want it just on what the maximum testing was for either sensitization on specific ingredients for the acid itself? Which information do you want?

DR. SHANK: We want the concentrations used for testing for sensitization to make sure that the old reports used the - - the studies done before used the concentrations that are applicable today. So if it's used at much higher concentration now, we can't use old reports at lower concentrations.

DR. MARKS: And the problem with that, Ron, is I mentioned earlier is that we only have irritation sensitization data in my review of zinc acetate. The other remaining zinc compounds, we have no irritation or sensitization so we're reading across - -

DR. SHANK: From just one.

DR. MARKS: One and then what we have - - let me see here. In this we have - -

DR. HILL: There are several other compounds that are mentioned in that section on irritation because you've got chloride's that irritating when you've got sulfate - -

DR. MARKS: We have sensitization data in this report - -

DR. HILL: I was talking about irritation. I'm sorry.

DR. MARKS: No, maybe we do have some. I'm sorry. I have the stearate. It's 10 percent with sulfate. Was that one of the old ones? No, I have - - we have some sensitization from this one here. Ten percent - - we do have a little, Ron. You're right. So let's bring that over. Do you want that as just a paragraph about this elaborating or do you want it the alternative method? You mentioned, Monice, was - -

MS. FIUME: So it would be, let's say zinc myristate but in the myristate acid and its salts, would there be information if you're going to read across because it dissociates so you're looking at - - worrying about the acid or - - Is there information in the old reports, other than just on zinc specifically that would be useful for the read across?

DR. MARKS: Right, I think that would be helpful.

MS. FIUME: So that might actually be easier in tabular form because of the large number of ingredients in those reports, if that's okay?

DR. MARKS: Yeah.

DR. SHANK: I think that's - - tag team.

DR. MARKS: That's good. Again, any other comments about these 28 zinc ingredients which tomorrow our team is going to move to issue a tentative report with a safe conclusion? Okay, if not, we'll move on

Safety Assessment of Zinc Salts as Used in Cosmetics

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The 2018 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Laura N. Scott, former Scientific Writer/Analyst, and Monice Fiume, Senior Director.

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (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. The 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.

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 Cosmetic Ingredient Review (CIR) Expert Panel (Panel) and determined to be safe for use in cosmetic products according to the use concentrations and practices specified in their respective safety assessments: Zinc Acetate (2012),[2] Zinc Citrate (2014),[3] Zinc Myristate (2010),[4] Zinc Ricinoleate (2007),[5] and Zinc Stearate (1982; reaffirmed in 2002).[6,7] When applicable, excerpts from the summaries of the reports on the previously reviewed ingredients are included in the text of this document, as appropriate, and are identified by *italicized text*. (This information is not included in the tables or the summary section.) For complete and detailed information, please refer to the original documents, which are available on the CIR website (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. 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), and the daily exposure from that food use is expected to result in a much larger systemic dose than that resulting from use in cosmetic products. Therefore, for GRAS ingredients, the focus of this report is on data other than oral toxicity and bioavailability (i.e., the focus is instead on local effects (e.g., dermal exposure and irritation and sensitization endpoints)).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (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 (U.S.) 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 1).

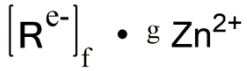


Figure 1. Zinc salts, wherein R is an anion and e*f = g*2

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

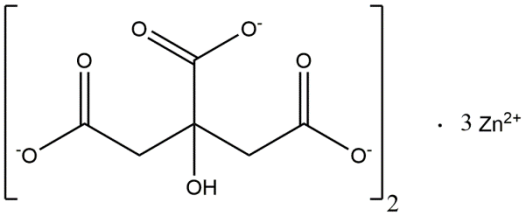


Figure 2. Zinc Citrate, an example salt (wherein R is citrate, e is 3 (1 for each "O^-"), f is 2, and g is 3)

Physical and Chemical Properties

Many of the zinc salts presented in this report are white or colorless crystalline solids, granules, or powders (Table 3). Formula weights range from 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/m^3.[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.[33] The mass median aerodynamic diameter (MMAD) of total dustiness (mono-modal 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%.

Zinc Stearate

According to the *FCC*, food grade specifications limit impurities in Zinc Stearate as follows: ≤ 10 mg (1.0%) residue weight of alkalies and alkaline earth metals, ≤ 1.5 mg/kg arsenic, ≤ 250 mg/kg chloride, ≤ 2 mg/kg lead, and ≤ 0.6% sulfate.[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 alkalies and alkaline earth metals, ≤ 2 mg/kg cadmium, ≤ 4 mg/kg lead, ≤ 5 mg/kg mercury, and ≤ 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 µg/ml.[61] In humans, most of the zinc is found in muscle and bones (~85%); total body zinc in men and women is approximately 2.5 and 1.5 g, respectively.[62] Smaller amounts of zinc are located in the skin and hair (~8%), liver (~5%), and gastrointestinal tract and pancreas (~3%).[36,63,64]

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 U.S. FDA are collected from manufacturers through the FDA Voluntary Cosmetic Registration Program (VCRP), and include the use of individual ingredients in cosmetics by cosmetic product category. The data received from the cosmetic industry are collected by the Personal Care Products Council (Council) in response to a survey of the maximum reported use concentrations by product category. VCRP data obtained from the FDA in 2017[65] and Council survey data collected in 2016 and 2017[66] 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).[65] 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).[65] 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).[67,68]

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;[65,67] 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 Lactate or Zinc Stearate.[66] 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 salt formula weights) that is used in oral care products or lipsticks is also included in Table 5. The greatest reported concentration of zinc present in oral care products is 0.2% via Zinc Stearate in a dentifrice, and the greatest concentration present in lipstick is 0.61% via Zinc Myristate.

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%)[67] and Zinc Stearate is reportedly used in baby lotions, oils, powders, and creams.[65]

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.[69-72] 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.[70,71] 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.[71] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Zinc Ascorbate, Zinc Chloride, Zinc Myristate, Zinc Stearate, Zinc Sulfate, and Zinc Undecylenate are reportedly used in face powders, dusting powders, or foot powders at concentrations between 0.02% to 20% and could possibly be inhaled. The VCRP indicates that Zinc Laurate is reportedly used in face powders.[65] 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.[73-75]

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%.[76] According to Annex IV/150, Zinc Stearate is included on the "list of colorants allowed in cosmetic products."[77]

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.[64,78,79] BfR confirmed the safety for adults of up to 1% zinc in toothpastes, however for mouthwashes containing zinc up to 1% they were concerned that regular use over an extended period of time may contribute to exceeding the "10% share of UL (upper limit)" for zinc. The BfR was also concerned about children and adolescents being at a more susceptible risk because of their lower body weights. Therefore, BfR proposed that the maximum zinc concentration in mouthwashes for adults not exceed 0.1% and that these products should not contain free zinc for people under the age of 18.

Cosmetics Europe conducted an aggregate exposure assessment, and in 2016 it was concluded that the 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 all ages.[64]

The European Commission Scientific Committee on Consumer Safety (SCCS) published a preliminary report in 2017 on the SCCS opinion on water-soluble zinc salts used in oral hygiene products.[64] The SCCS concluded that exposure estimates to water-soluble zinc salts in toothpastes (1%) and mouthwashes (0.1%) could potentially result in daily intakes of 3.54 mg for adults and children (7-17 years). This would be 14% (adults) and 27% (children) of the recommended 25 mg/day upper limit for zinc; the SCCS considered these to be safe usages in oral hygiene products. In children up to 6 years of age, the SCCS estimated that water-soluble zinc salts exposure in toothpastes (1%) may result in daily intakes between 1.0 and 2.0 mg, which would be 10% and 29% of the recommended upper limit; the SCCS concluded that this would be a safe usage in toothpastes. The use of mouthwash is not recommended in children under 6 years of age. The SCCS also noted that it could not advise on the percentage of the zinc upper limit to attribute to cosmetic exposure. However, the SCCS did acknowledge that in children up to 17 years of age, depending on dietary exposure to zinc, it may be possible that aggregate zinc intake could exceed the upper limit.

Non-Cosmetic

The uses of many zinc salts, as specified in 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 U.S., Zinc Chloride, Zinc Gluconate, Zinc Stearate, and Zinc Sulfate are GRAS as direct food additive (nutritive) intended for human consumption when used with good manufacturing practice (21CFR182.8985, 21CFR182.8988, 21CFR182.8994, 21CFR182.8997).

The U.S. recommended dietary allowances (RDAs) for zinc are 11 mg/day 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) 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 Health Organization (WHO) lists Zinc Sulfate (20 mg solid form) 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), 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) 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).[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 cream[44] and wound cleanser[46] and Zinc Gluconate (0.02%) was listed as an active ingredient (breath freshener) in a mouthwash[47] 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 human 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 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 membranes is important to maintain cellular and subcellular zinc homeostasis.[86] Although zinc ions can cross 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 for 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 was potentially 1.6%; 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 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 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 enterocytes 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.[63,64] 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 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 ^{65}Zn was similar with all three substances, ranging from 40-48%.[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 LD_{50} of an eye shadow formulation that contained 10% Zinc Stearate was >2000 g/kg .[6] The oral LD_{50} of Zinc Stearate is >5 g/kg in rats. The inhalation LC_{50} of Zinc Stearate following a single 1 h exposure was >200 mg/l in rats; 1 animal died.

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

The dermal LD_{50}s of Zinc Stearate (in rabbits)[63] and Zinc Sulfate (in rats)[19,25,31] are >2000 mg/kg. Reported oral LD_{50}s are 287 mg/kg Zinc Acetate (dihydrate) in mice,[95] 794 mg/kg Zinc Acetate (dihydrate) is in rats,[95] between 500 mg/kg and 2000 mg/kg Zinc Lactate in rats,[25] 926 mg/kg Zinc Nitrate (hexahydrate) in mice,[95] 1330 mg/kg Zinc Nitrate (hexahydrate) in rats,[95] > 5000 mg/kg Zinc Phosphate in rats,[22] > 2000 mg/kg Zinc Ricinoleate in rats,[26] and > 5000 mg/kg Zinc Stearate in rats.[63] In inhalation studies, reported LC_{50}s in rats are 2000 mg/m^3 Zinc Chloride,[25] and > 5.08 mg/L air Zinc Laurate.[33] In dogs and sheep, inhalation exposure to ≤ 5.18 mg/m^3 (1%) and ≤ 8.3 mg/m^3 (0.5%) Zinc Sulfate, respectively, for up to 4 h did not affect lung function (dogs) or tracheal mucous velocity (sheep).[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) was added to drinking water of rats, a no-observed-effect-level (NOEL) of 160 mg/kg/day was reported; concentrations of zinc were statistically significantly higher in several organs and the blood of animals of the mid- and high-dose groups.[24,97] In a 13-wk feed study of Zinc Sulfate, a NOEL of 3000 ppm was reported in mice and rats; some mice (but no rats) dosed with 30,000 ppm died, and numerous toxic effects were reported in both mice and rats of the 30,000 ppm groups.[21,98] No significant toxicologic effects or pulmonary or cardiac changes were reported in an inhalation study in rats exposed to 100 µg/m^3 water soluble Zinc Sulfate for 5 h/day for 3 days/week for 16 wks.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Zinc is a very important element in the reproductive cycle of 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 zinc 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 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 for 84 days (premating through lactation), adverse effects were reported in the dams and the offspring, including a reduced number of live pups/litter, a decreased live birth index, increased mortality, and increased fetal resorption.[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, the overall no-observed-adverse-effect-level (NOAEL) was 7.5 mg/kg/day for the F_1 generation.[25,101] Parental animals from F_0 and F_1 generations had reduced fertility and viability, and effects on organ weights were reported in parental animals; reduced body weights were reported for F_1 and F_2 pups in 30 mg/kg/day group, however no effects on weaning index, sex ratio, or litter size observed. The developmental and reproductive effects of Zinc Sulfate were examined in mice (≤ 30 mg/kg/day; days 6-15 of gestation),[21] rats (up to 42.5 mg/kg; days 6-15 of gestation),[102] hamsters (≤ 88 mg/kg/day; days 6-10 of gestation),[20,31] and rabbits (≤ 60 mg/kg; 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 µg/plate),[105] unscheduled DNA synthesis (UDS) assay in rat hepatocytes (≤ 1000 µg/ml), and in human lymphocytes,[106] but it was positive in a mouse lymphoma assay in a dose-dependent manner (1.3 - 13 µg/ml without and 4.2 - 42 µg/ml with metabolic activation)[105] and in a chromosomal aberration assay in Chinese hamster ovary (CHO) cells (25 - 45 µg/ml without and 45 - 80 µg/ml with metabolic activation). Zinc Chloride was not mutagenic in an Ames test (≤ 100 mg/l),[107] a mouse lymphoma assay (≤ 12.13 µg/ml),[108] or chromosomal aberration assay in human dental pulp cells (≤ 300 µM);[82] it was genotoxic in a clastogenicity study in human peripheral blood leukocytes [109] and in a micronucleus assay with human peripheral blood lymphocytes (at 100 mg/l),[107] it was positive in a cytokinesis-block micronucleus assay,[110] and 3.2 mM caused a 2-fold increase in λ-prophage induction in *Escherichia coli* WP2 as compared to controls.[25] Zinc Nitrate (≤ 1 mM),[111] Zinc Stearate (concentrations not specified),[27] and Zinc Sulfate (≤ 3600 µg/plate)[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 *Saccharomyes 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),[112] in sperm-head abnormalities (≤ 15 mg/kg), and in a Comet assay (eukaryotic cells; ≤ 19.95 mg/kg).[113]

CARCINOGENICITY

Animal

Chester Beatty mice were administered Zinc Sulfate (heptahydrate; 1000 ppm and 5000 ppm) in their drinking water for 45 to 53 weeks. Controls were used, however some died due to a viral infection and were, therefore, replaced with additional control animals (no further details).[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) was added to the cell culture. Colonies from these cell cultures were prepared for counting 8 to 9 days following seeding of the target cells. A similar experiment was conducted with a known carcinogenic promoter, benzo[a]pyrene (3.2 µM), in cell cultures both with and without the addition of Zinc Chloride. Control cell cultures to which neither Zinc Chloride nor benzo[a]pyrene were added or only benzo[a]pyrene was added were also examined. The transformation frequencies reported were 0%, 0.7%, 0%, and 0.4% for control (without Zinc Chloride or benzo[a]pyrene), benzo[a]pyrene only, Zinc Chloride only, and Zinc Chloride plus benzo[a]pyrene, respectively. The study researchers concluded that Zinc Chloride did not induce transformation on its own or enhance transformation when benzo[a]pyrene was present.

Another transformation assay conducted in Syrian hamster embryo cells (13 to 14 days into gestation) showed that Zinc Chloride (up to 20 µg/ml of appropriate medium) did not induce morphological transformation after cells were exposed to the test substance for 7 to 8 days; Zinc Chloride was reported to reduce the cloning efficiency by 20 to 25%.[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) in their drinking water daily for 4 days prior to depilation or spontaneous anagen induction and up to 28 days to 1 year during hair follicle cycling. Unadulterated drinking water was administered to control animals. Hair pigmentation was evaluated using electron paramagnetic resonance (EPR) to detect melanin. There was a 10% drop in body weight in treated animals, but it reversed after 2 weeks and was thought by study researchers to be caused by decreased water intake. During spontaneous and depilation-induced hair growth cycles it was noted that hair pigmentation turned from the normal black to a bright brown in treated animals, which was not observed in controls. This was correlated with dose-dependency, but not attributed to a change in quality of melanin. Pigment generation was not transferred from eumelanogenesis to phaeomelanogenesis. EPR testing showed that Zinc Sulfate treatment inhibited anagen-coupled eumelanogenesis. After completion of a full hair cycle, skin and hair shaft melanin content was statistically significantly reduced in treated compared to control animals; hair shaft depigmentation was observed during multiple hair cycles in treated animals.

Corneal Wound Healing

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 mm^2 samples of the corneas were removed, dyed and digitally analyzed to determine the extent of corneal wound healing up to 36 hours after corneal epithelial abrasion occurred. Corneal wound healing improved with decreasing concentrations of Zinc Chloride. Notably by 24 hours following corneal abrasion, the 0.0010% and 0.0025% concentrations showed statistically significant improvement of > 90% corneal wound healing compared to the saline control samples which showed 83% healing, based on the means of 4 to 11 rat corneas.

DERMAL IRRITATION AND SENSITIZATION STUDIES

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 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 CIR 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] in 70% squalene; n= 55 and 52, respectively), Zinc Laurate (7% in formulation; n=104),[126] and Zinc Myristate (in formulation, effective test concentration 14% in 70% squalene; 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 CIR 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

In a Health Professionals Follow-Up Study, researchers evaluated the association of supplemental zinc consumption and risk of prostate cancer in 46,974 men in the United States.[129] In the 14 years (1986 - 2000) of follow-up, there were 2901 new cases of prostate cancer. Of the new cases, 434 were advanced cancer. Study researchers observed that there was no association with prostate cancer risk in those who consumed supplements of 100 mg zinc (usually in the form of Zinc Gluconate) or less per day. Compared to men who did not consume zinc supplements, those who supplemented with more than 100 mg/day zinc showed a 2.29 (95% confidence interval of 1.06 to 4.95, p = 0.003) relative risk in advanced prostate cancer. The risk increased to 2.37 (95% confidence interval of 1.42 to 3.95, p = 0.001) for men who supplemented with zinc for 10 years or more. The study researchers noted that there could be confounding factors such as calcium intake supplementation or another unmeasured correlation related to zinc supplementation.

Zinc Chloride

In humans, inhalation exposure via aerosol (exposure duration not specified) to 40 mg/m^3 Zinc Chloride (19.2 mg/m^3 zinc) produced a metallic taste; the particle size and other details were not provided.[63] Another study reported that in human subjects exposed via inhalation to 4800 mg/m^3 Zinc Chloride for 30 minutes, pulmonary effects were induced (no further details).

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,[130-132] but not all,[133] 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),[134] sometimes resulting in death, after inhalation of Zinc Chloride from a smoke bomb.[134-141] In a case where a patient survived, corticosteroid treatment and extracorporeal life support measures were followed.[135]

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.[142] 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 adults[143-145] and children.[146-149] 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).[143] 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.[146-148] A 10-year-old girl developed an antral stricture in her stomach 3 weeks following accidental ingestion of a soldering flux solution containing Zinc Chloride (30% to < 60%) and underwent Heineke-Mikulicz antropyloroplasty with an uneventful recovery, although on follow-up delayed gastric emptying was noted.[147] Chelation therapy in children and adults was initiated if systemic toxicity persisted or when serum zinc levels were elevated.[145,146,148,149]

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.[150] 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]

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 wINCI *Dictionary*, these ingredients have many functions in cosmetics including hair conditioning agents, skin conditioning agents, cosmetic astringents, cosmetic biocides, preservatives, oral care agents, buffering agents, bulking agents, chelating agents, and viscosity increasing agents.

VCRP data obtained from the U.S. FDA and data received in response to a survey of the maximum reported use concentration by product category conducted by the Council indicate that 18 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 of the zinc salts are used in cosmetics that are 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 0.2% via Zinc Stearate in a dentifrice, and the greatest concentration present in lipstick is 0.61% via Zinc Myristate

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 U.S., Zinc Chloride, Zinc Gluconate, Zinc Stearate, and Zinc Sulfate are GRAS as direct food additive (nutritive) intended for human consumption when used with good manufacturing practice. GRAS status (U.S.) was established for Zinc Acetate, Zinc Carbonate, Zinc Chloride, Zinc Gluconate, Zinc Stearate, and Zinc Sulfate with the use of good manufacturing and feeding practices in animals.

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

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 40-48%. In a study examining the distribution of zinc to different organs after a single oral administration of Zinc Chloride in rats, it was determined that zinc was mainly accumulated in small intestine, liver, kidneys and large intestine. In human subjects that were given a single oral dose of 50 mg elemental zinc as the acetate salt under either high (pH > 5) or low (pH < 3) intragastric pH conditions, absorption was faster with low intragastric pH.

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

In a 3-mo study in which 160 – 640 mg/kg/day Zinc Acetate (dihydrate) was added to drinking water of rats, a NOEL of 160 mg/kg/day was reported; concentrations of zinc were statistically significantly higher in several organs and the blood of animals of the 640 mg/kg/day groups. In a 13-wk feed study of Zinc Sulfate, a NOEL of 3000 ppm was reported in mice and rats; some mice (but no rats) dosed with 30,000 ppm died, and numerous toxic effects were reported in both mice and rats of the 30,000 ppm groups. No significant toxicological effects or pulmonary or cardiac changes were reported in an inhalation study in rats exposed to 100 µg/m^3 water soluble Zinc Sulfate for 5 h/day for 3 days/week for 16 wks. In a study in which human subjects were given a supplement with 15 or 100 mg/day zinc, supplied as Zinc Acetate, for 3 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.

Zinc is a very important element in the reproductive cycle of some species. 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.

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

Both positive and negative results were reported in genotoxicity studies of zinc salts. In in vitro studies, Zinc Acetate was negative in an Ames test (≤ 7200 µg/plate), UDS assay in rat hepatocytes (≤ 1000 µg/ml), and in human lymphocytes, but it was positive in a mouse lymphoma assay in a dose-dependent manner (1.3 - 13 µg/ml without and 4.2 - 42 µg/ml with metabolic activation) and in a chromosomal aberration assay in CHO cells (25 - 45 µg/ml without and 45 - 80 µg/ml with metabolic activation). Zinc Chloride was not mutagenic in an Ames test (≤ 100 mg/l), a mouse lymphoma assay (≤ 12.13 µg/ml), or chromosomal aberration assay in human dental pulp cells (≤ 300 µM); it was genotoxic in a clastogenicity study in human peripheral blood leucocytes and in a

micronucleus assay with human peripheral blood lymphocytes (at 100 mg/l), in a cytokinesis-block micronucleus assay, and 3.2 mM caused 2-fold increase in λ-prophage induction in *Escherichia coli* WP2 as compared to controls. Zinc Nitrate ≤ 1 mM),[111] Zinc Stearate (concentrations not specified),[27] and Zinc Sulfate (≤3600 µg/plate)[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 *Saccharomyes cerevisiae* diploid strain D4. Zinc Chloride was genotoxic in several in vivo assays using mice; statistically significant, dose-dependent increases were observed in chromosomal aberrations of bone-marrow cells (≤ 15 mg/kg), in sperm-head abnormalities (≤ 15 mg/kg), and in a Comet assay (eukaryotes; ≤ 19.95 mg/kg).

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

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

Zinc Sulfate, administered up to 1200 mg/kg in the drinking water of mice, resulted in a statistically significantly reduction in skin and hair shaft melanin content.

In a 5-day open patch study, Zinc Acetate (20% in deionized water) was irritating in mouse skin, non-irritating in guinea pig, and slightly irritating in rabbit skin, Zinc Chloride (1% in deionized water) was severely irritating in mouse and rabbit skin and irritating in guinea pig skin, Zinc Sulfate (1% in deionized water) was slightly irritating in all three species, and Zinc Undecylenate (20% in 0.1% Tween 80 vehicle) was slightly irritating in mouse and rabbit skin and non-irritating in guinea pig skin. The test substances were also evaluated in a closed patch test in rabbits that included a 3-day patch followed by a 2-day patch; Zinc Acetate and Zinc Chloride were severely irritating and Zinc Sulfate and Zinc Undecylenate were slightly irritating. Four h patches of Zinc Lactate (occlusive), Zinc Neodecanoate (semi-occlusive), Zinc Ricinoleate (occlusive), and Zinc Sulfate (semi-occlusive) were non-irritating to rabbit skin; the test materials were applied undiluted. A single application of Zinc Nitrate resulted in pronounced skin irritation in rats, rabbits, and guinea pigs; details were not provided. In clinical testing, Zinc Gluconate (0.05% in formulation) and Zinc Undecylenate (0.25% 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/m^3 Zinc Chloride (19.2 mg/m^3 zinc) produced a metallic taste; the particle size and other details were not provided. Another study reported that in human subjects exposed via inhalation to 4800 mg/m^3 Zinc Chloride for 30 minutes, pulmonary effects were induced (no further details).

There are case reports in the literature of poisonings following oral ingestion of large amounts of Zinc Chloride in adults and children. In one case report, a patient had multiple pruritic eruptions over his whole body; the patient had his teeth filled 3 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.

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 zinc ion drives the chemistry of these ingredients, and the lack of chemical reactivity accounts for biocompatibility. 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.

[***Please consider providing language for the following Discussion items:***

- ***exposure through oral care products***
- ***DART results***

- ***mixed genotoxicity results***
- ***any concern regarding results of Prospective Study and prostate cancer]***

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, 95% – 99% of 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 http://www.cir-safety.org/cir-findings

CONCLUSION

The CIR Expert Panel 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.*

TABLES

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

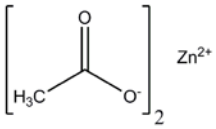
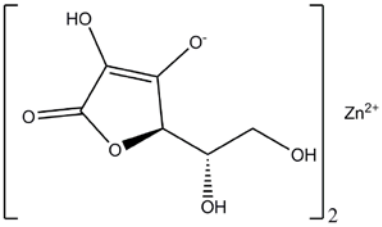
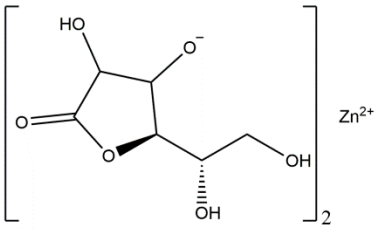
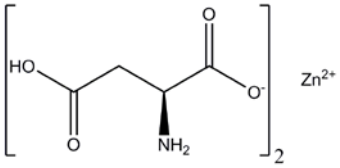
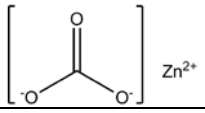
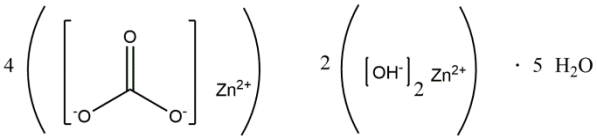
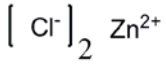
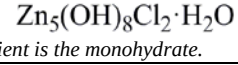
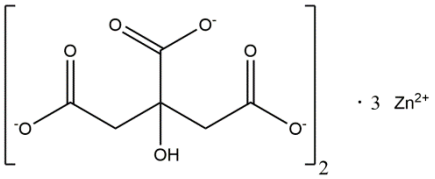
Ingredient CAS No.	Definition & Structure	Function
Zinc Acetate 557-34-6 (anhydrous) 5970-45-6 (hydrate)	Zinc Acetate is the zinc salt of acetic acid that conforms to the formula: 	cosmetic astringents; cosmetic biocides; skin protectants
Zinc Ascorbate 134343-96-7	Zinc Ascorbate is the zinc salt of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

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

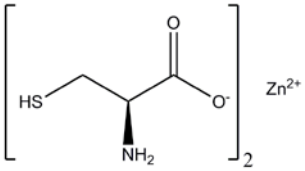
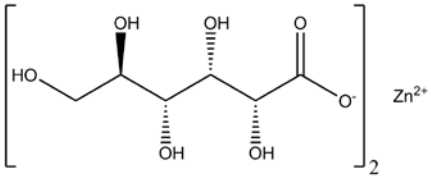
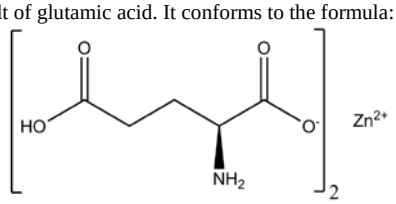
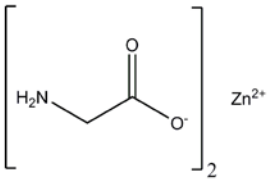
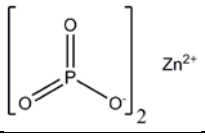
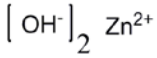
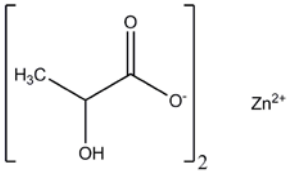
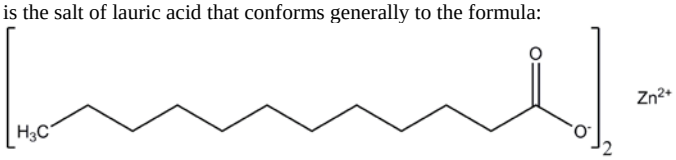
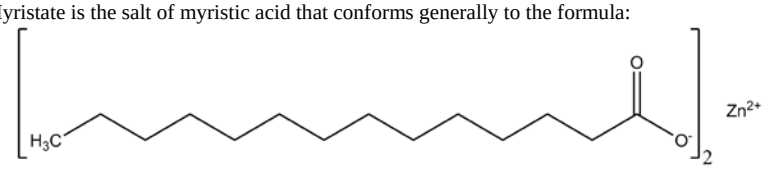
Ingredient CAS No.	Definition & Structure	Function
Zinc Cysteinate 1197186-61-0	Zinc Cysteinate is the organic salt that conforms to the formula: 	cosmetic biocides
Zinc Gluconate 4468-02-4	Zinc Gluconate is the zinc salt of gluconic acid that conforms to the formula: 	cosmetic biocides; skin-conditioning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

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

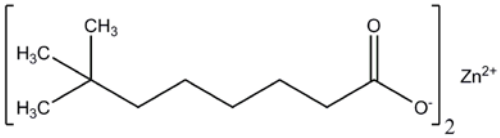
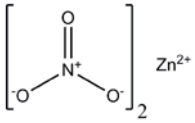
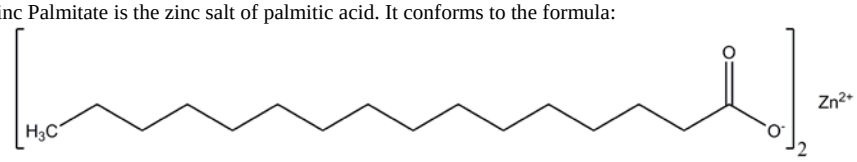
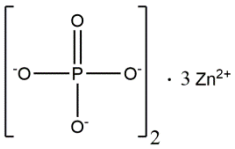
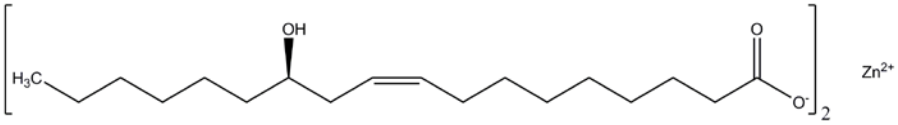
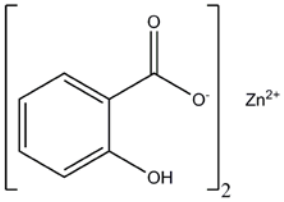
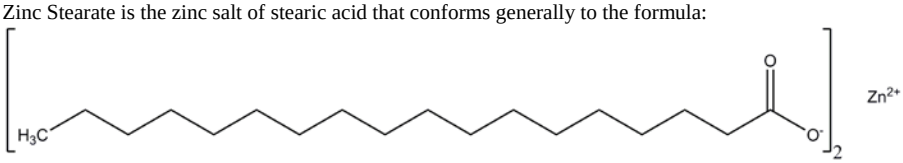
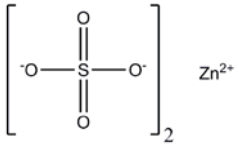
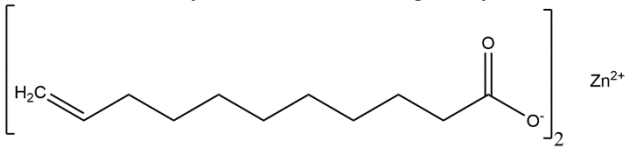
Ingredient CAS No.	Definition & Structure	Function
Zinc Neodecanoate 27253-29-8	Zinc Neodecanoate is the zinc salt of neodecanoic acid. It conforms generally to the formula: 	anticaking agents; viscosity increasing agents-non-aqueous
Zinc Nitrate 7779-88-6	Zinc Nitrate is the inorganic salt that conforms to the formula: 	skin-conditioning agents-miscellaneous
Zinc Palmitate 4991-47-3	Zinc Palmitate is the zinc salt of palmitic acid. It conforms to the formula: 	anticaking agents; slip modifiers; viscosity increasing agents-non-aqueous
Zinc Phosphate 7543-51-3	Zinc Phosphate is the inorganic compound that conforms to the formula: 	buffering agents; oral care agents
Zinc Ricinoleate 13040-19-2	Zinc Ricinoleate is the zinc salt of Ricinoleic Acid that conforms to the formula: 	anticaking agents; deodorant agents; opacifying agents
Zinc Salicylate 16283-36-6	Zinc Salicylate is the organic compound that conforms to the formula: 	Preservatives
Zinc Stearate 557-05-1	Zinc Stearate is the zinc salt of stearic acid that conforms generally to the formula: 	anticaking agents; colorants; slip modifiers; viscosity increasing agents-non-aqueous
Zinc Sulfate 7446-19-7 (monohydrate) 7446-20-0 (heptahydrate) 7733-02-0 (anhydrous)	Zinc Sulfate is the inorganic salt that conforms to the formula: 	cosmetic astringents; cosmetic biocides; oral care agents
Zinc Undecylenate 557-08-4	Zinc Undecylenate is the salt of undecylenic acid that conforms generally to the formula: 	anticaking agents; antifungal agents; cosmetic biocides

Table 2. Conclusions and dermal irritation and sensitization data and ocular irritation data for constituent acids and related salts previously reviewed by the Panel

Ingredient	Conclusion (year issued)* and dermal and ocular data	Reference
	CONSTITUENT ACIDS	
Acetic Acid	Safe in the present practices of use and concentration (2012) Irritation/sensitization: glacial acetic acid (equivalent to 95% Acetic Acid) caused complete destruction of the skin of guinea pigs afer 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 Ocular: >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) Irritation/sensitization: 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 Ocular: no data reported	8
Aspartic Acid	Safe in the present practices of use and concentration (2013) Irritation/sensitization: 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 Ocular: 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) Irritation/sensitization: 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 anigoedema patients Ocular: 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) Irritation/sensitization: a 50% aq. solution of Gluconic Acid was not a dermal irritant in rabbits Ocular: 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) Irritation/Sensitization: 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 Ocular: no data reported	
Lactic Acid	Safe for use at concentrations ≤ 10%, at final formulation pH ≥ 3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection; safe for use in salon products at concentrations ≤ 30%, at final formulation pH ≥ 3.0, in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection (1998); reaffirmed in 2013 Irritation/Sensitization: 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. Ocular: 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 lo-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; f ace and hair products containing 0.l-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

Table 2. Conclusions and dermal irritation and sensitization data and ocular irritation data for constituent acids and related salts previously reviewed by the Panel

Ingredient	Conclusion (year issued)* and dermal and ocular data	Reference
Lauric Acid	Safe in the present practices of use and concentration (1987); reaffirmed 2006 Irritation/sensitization: in a HRIPT, 1% Lauric Acid in formulation was not an irritating or sensitizer Ocular: 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 cornea1 opacity, mild conjunctivitis, iritis	12,13
Myristic Acid	Safe in the present practices of use and concentration (2010) Irritation/sensitization: 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 Ocular: in rabbits, formulations containing 1.5-50% Myristic Acid, and Myristic Acid as commercially supplied, were not irritants	4,12,13
Palmitic Acid	Safe in the present practices of use and concentration (1987); reaffirmed 2006 Irritation/sensitization: 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 Ocular: 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) Irritation/sensitization: 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. Ocular: 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) Irritation/sensitization: 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 Ocular: no data reported	14
Stearic Acid	Safe in the present practices of use and concentration (1987); reaffirmed 2006 Irritation/Sensitization: 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 0.5-13% Ocular: in rabbits, formulations containing 1-65% Stearic Acid, and Stearic Acid as commercially supplied, wasw at mot 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

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

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

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, alkalies, 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		
Formula Weight (g/mol)	117.837 (est.)	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)	305.69	161
Log P	-7.50 (est.)	153
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

Table 3. Physical and Chemical Properties

Property	Value	Reference
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 MMAD of total dustiness: 8.50 µm; GSD of MMAD: 4.36	33
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
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

Table 3. Physical and Chemical Properties

Property	Value	Reference
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]

Table 5. Frequency and concentration of use according to duration and type of exposure for zinc salts[2-5,7,65,66]

	# 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**	**2**	**1.6**	**76**	**0.000095-0.47**
Duration of Use						
Leave-On	*8*	*NR*	*2*	*NR*	*62*	*0.0001-0.47*
Rinse-Off	*17*	*NR*	*NR*	*1.6*	*14*	*0.000095-0.21*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	1	NR	1	NR	8	0.039-0.064
Incidental Ingestion	NR	NR	NR	NR	9	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: 15[a], 3[b]	spray: NR possible: 0.003-0.088[a]
Incidental Inhalation-Powder	powder: NR possible: 2[b]	NR	powder: NR possible: 1[b]	NR	powder: NR possible: 3[b]	powder: 0.04-0.47 possible: NR
Dermal Contact	9	NR	2	NR	64	0.00075-0.47
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	16	NR	NR	1.6	3	0.000095-0.21
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	9	oral care: 0.088 (0.041% Zn)
Baby Products	NR	NR	NR	NR	NR	NR

Table 5. **Frequency and concentration of use according to duration and type of exposure for zinc salts**[2-5,7,65,66]

	# of Uses	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*
	Zinc Citrate****		**Zinc Citrate**		**Zinc Gluconate**	
	2011	***2011***	**2017**	**2016**		
Totals*	***9***	***0.05-2***	**13**	**0.05-2**	**318**	**0.000005-3**
Duration of Use						
Leave-On	*5*	*0.05*	*5*	*NR*	*243*	*0.00024-3*
Rinse-Off	*4*	*0.3-2*	*8*	*0.05-2*	*73*	*0.00005-0.5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*2*	*0.000005*
Exposure Type						
Eye Area	*NR*	*NR*	NR	NR	35	0.0048-3
Incidental Ingestion	*4*	*0.3-2*	8	oral care: 0.28-2 (0.031 - 0.22% Zn)	10	lipstick: 0.1 (0.031% Zn)
Incidental Inhalation-Spray	*NR*	*NR*	NR	spray: NR possible: 0.28[a]	spray: NR possible: 76[a], 65[b]	spray: NR possible: 0.001[a]
Incidental Inhalation-Powder	*NR*	*powder: 0.05*	NR	NR	powder: NR possible: 65[b]	powder: NR possible: 0.001-1[c]
Dermal Contact	*5*	*0.05*	5	0.05	282	0.000005-3
Deodorant (underarm)	*4*[a]	*NR*	3[a]	NR	14[a]	NR
Hair - Non-Coloring	*NR*	*NR*	NR	NR	22	0.00005-0.5
Hair-Coloring	*NR*	*NR*	NR	NR	4	NR
Nail	*NR*	*NR*	NR	NR	NR	NR
Mucous Membrane	*4*	*0.3-2*	8	oral care: 0.28-2 (0.031-0.22% Zn) not oral: 0.05	19	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**	**1**	**0.25-1.8**
Duration of Use						
Leave-On	*NR*	*0.009*	*2*	*NR*	*NR*	*NR*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*1*	*0.25-1.8*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	1	oral care: 0.25-0.44 (0.065-0.12% Zn)
Incidental Inhalation-Spray	NR	NR	spray: NR possible: 1[a], 1[b]	NR	spray: NR possible: 1[a]	spray: NR possible: 0.25[a]
Incidental Inhalation-Powder	NR	NR	powder: NR possible: 1[b]	NR	NR	NR
Dermal Contact	NR	0.009	2	NR	NR	1.8
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	1	oral care: 0.25-0.44 (0.065-0.12% Zn)
Baby Products	NR	NR	NR	NR	NR	NR

Table 5. Frequency and concentration of use according to duration and type of exposure for zinc salts[2-5,7,65,66]

	# of Uses	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*
	Zinc Laurate		***Zinc Myristate****		**Zinc Myristate**	
	2017	**2016**	***2007***	***2006***	**2017**	**2016**
Totals*	**115**	**1-7**	***122***	***0.00005-20***	**59**	**0.005-20**
Duration of Use						
Leave-On	*97*	*1-7*	*122*	*0.00005-20*	*59*	*0.005-20*
Rinse-Off	*17*	*1.2*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*1*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	56	NR	*60*	*0.05-6*	25	0.51-20
Incidental Ingestion	NR	NR	*NR*	*5*	NR	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: 18 possible: NR	powder: 2-20 possible: 5-15[c]
Dermal Contact	105	1-7	*117*	*0.001-20*	59	0.51-20
Deodorant (underarm)	NR	NR	*NR*	*NR*	NR	NR
Hair - Non-Coloring	10	NR	*NR*	*NR*	NR	NR
Hair-Coloring	NR	NR	*NR*	*NR*	NR	NR
Nail	NR	NR	*5*	*0.00005*	NR	0.005-0.035
Mucous Membrane	5	NR	*NR*	*5*	NR	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***	**27**	**0.15-2.3**
Duration of Use						
Leave-On	*NR*	*NR*	*2*	*1-2*	*25*	*0.15-2.3*
Rinse-Off	*NR*	*1*	*1*	*NR*	*2*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	*NR*	*NR*	NR	NR
Incidental Ingestion	NR	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*	23	0.15-2.3
Deodorant (underarm)	NR	NR	*2[a]*	*2[a]*	21[a]	spray: 0.82-2.3 not spray: 0.82-2
Hair - Non-Coloring	NR	NR	*NR*	*1*	NR	NR
Hair-Coloring	NR	NR	*NR*	*NR*	NR	NR
Nail	NR	NR	*NR*	*NR*	1	NR
Mucous Membrane	NR	oral care: 1 (0.17% Zn)	*NR*	*NR*	3	lipstick: 1.1 (0.11% Zn)
Baby Products	NR	NR	*NR*	*NR*	NR	NR

Table 5. Frequency and concentration of use according to duration and type of exposure for zinc salts[2-5,7,65,66]

	# of Uses	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*
	Zinc Salicylate		***Zinc Stearate***		**Zinc Stearate**	
	2017	**2016**	***2001***	***2001***	**2017**	**2016**
Totals*	**NR**	**0.47**	***746***	***0.5-51***	**2321**	**0.2-32**
Duration of Use						
Leave-On	*NR*	*0.47*	*742*	*0.5-51*	*2312*	*0.2-32*
Rinse-Off	*NR*	*NR*	*2*	*1*	*7*	*0.28-3.3*
Diluted for (Bath) Use	*NR*	*NR*	*2*	*3*	*2*	*NR*
Exposure Type						
Eye Area	NR	NR	*346*	*1-16*	1397	1-32
Incidental Ingestion	NR	NR	*2*	*3*	5	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: 10[a], 8[b]	spray: 0.3 possible: NR
Incidental Inhalation-Powder	NR	NR	*powder: 236 possible: 5[b], 2[c]*	*powder: 2-24 possible: 1-2[b], 0.5[c]*	powder: 456 possible: 8[b], 1[c]	powder: 1.1-14 possible: 0.2-1[c]
Dermal Contact	NR	0.47	*738*	*0.5-51*	2308	0.2-32
Deodorant (underarm)	NR	not spray: 0.47	*NR*	*2[a]*	NR	NR
Hair - Non-Coloring	NR	NR	*1*	*NR*	NR	NR
Hair-Coloring	NR	NR	*NR*	*NR*	6	3.3
Nail	NR	NR	*NR*	*NR*	NR	NR
Mucous Membrane	NR	NR	*4*	*3*	7	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*	**134**	**0.0001-1**	**NR**	**0.25**
Duration of Use				
Leave-On	*75*	*0.0001-1*	*NR*	*0.25*
Rinse-Off	*59*	*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: 14[a], 20[b]	spray: NR possible: 0.003[a]	NR	spray: NR possible: 0.25[b]
Incidental Inhalation-Powder	powder: 5 possible: 20[b]	powder: 0.02 possible: 0.0008-0.12[c]	NR	powder: NR possible: 0.25[b]
Dermal Contact	101	0.0003-1	NR	0.25
Deodorant (underarm)	NR	0.0015	NR	NR
Hair - Non-Coloring	32	0.003-0.15	NR	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	0.0001-0.001	NR	NR
Mucous Membrane	13	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; use from previous report is included for comparison.
*** Frequency of use data from the VCRP was reported separately for Zinc Sulfate and zinc sulfate anhydrous, but the above frequency of use totals for Zinc Sulfate are the sum of uses for both forms of the ingredient.
[a] Includes products that can be sprays, but it is not known whether the reported uses are sprays.
[b] Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation.
[c] Includes products that can be powders, but it is not known whether the reported uses are powders.
NR – no reported use.

Table 6. Ingredients Not Reported to Be in Use[65,67,68]

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

Table 7. Appearance of Ingredients in Code of Federal Regulations

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

Table 7. Appearance of Ingredients in Code of Federal Regulations

Ingredient	Non-Cosmetic Use	References*
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
Zinc Salicylate	-Indirect food additive; Zinc Salicylate may be used as an antioxidant and/or stabilizer in polymers with the stipulation to be used in only rigid polyvinyl chloride polymers or copolymers and total salicylates (calculated as acid) ≤ 0.3% by weight in these polymers	21CFR178.2010
Zinc Stearate	-Indirect food additive, paper and paperboard components	21CFR176.180
	-Indirect food additive, polymers, food contact surfaces, melamine-formaldehyde resins (1:3 molar ratio of melamine to formaldehyde in aqueous solution); urea-formaldehyde resins (1:2 molar ratio of urea to formaldehyde in aqueous solution); phenolic resins; Zinc Stearate may be used as a lubricant in these resins	21CFR177.1460; 21CFR177.1900; 21CFR177.2410
	-Indirect food additive; Zinc Stearate may be used as antioxidant and/or stabilizer in polymers	21CFR178.2010
	-Zinc Stearate is GRAS as a nutrient used for human consumption when used with GMP	21CFR182.8994
	-Requirements for specific new drugs or devices; drug products containing certain active ingredients offered OTC; there are inadequate data to establish safety and effectiveness of Zinc Stearate in topical acne drug products	21CFR310.545
	-Interpretative statements re warnings on drugs and devices for OTC sale, warning and caution statements for drugs; Zinc Stearate dusting powders has the following recommended warning and caution statement: "Keep out of reach of children; avoid inhaling. If swallowed, get medical help or contact a Poison Control Center right away."	21CFR369.20
	-Zinc Stearate (prepared from stearic acid not containing chick-edema factor) is GRAS as a nutrient or dietary supplement for animals when using GMP or feeding practice	21CFR582.5994
	-Occupational safety and health standards, toxic and hazardous substances, air contaminants; Zinc Stearate shall not exceed the 8-hour Time Weighted Average in any 8-hour work shift of a 40-hour work week; Zinc Stearate air contaminant limits are total dust (15 mg/m^3) and respirable fraction (5 mg/m^3)	29CFR1910.1000; 29CFR1915.1000
Zinc Sulfate	-Zinc Sulfate is GRAS as a substance migrating to food from paper and paperboard products in food packaging	21CFR182.90
	-Zinc Sulfate is GRAS as a nutrient used for human consumption when used with GMP	21CFR182.8997
	-Requirements for specific new drugs or devices; drug products containing certain active ingredients offered OTC; there are inadequate data to establish safety and effectiveness of Zinc Sulfate in the following types of drug products: external analgesic and anesthetics, specifically for treatment of fever blister and cold sores; poison treatment; astringents	21CFR310.545
	-Ophthalmic drug products for OTC human use; Zinc Sulfate (0.25%) may be used as an active ingredient in ophthalmic astringents	21CFR347.50
	-New animal drugs for use in animal feeds; Zinc Sulfate (variable concentration, 0.76% or 1.47%) may be used in free-choice animal feed containing fenbendazole given to cattle	21CFR558.258
	-Zinc Sulfate (hydrated or anhydrous forms) is GRAS as a trace mineral added to animal feeds using good feeding practice	21CFR582.80; 21CFR582.5997

Table 7. Appearance of Ingredients in Code of Federal Regulations

Ingredient	Non-Cosmetic Use	References*
Zinc Undecylenate	-Topical antimicrobial drug products for OTC human use; Zinc Undecylenate (total undecylenate concentration of 10% to 25%) may be used as an active ingredient in topical antifungal drug products	21CFR333.210

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

Table 8. Dermal Penetration Studies

Test Substance(s)	Species	Sample Type or Test Population	Dose/Concentration	Procedure	Results	Reference
DERMAL PENETRATION						
IN VITRO						
Animal						
Zinc Sulfate (monohydrate)	Pig	Stratum corneum, stratum germinativum, and blood vessel containing dermis collected using a dermatome; n=6 skin samples evaluated (no further details provided)	40 mg/ml in water, 1 mg/cm^2 concentration applied to skin samples	Skin samples prepared at 1 mm thickness and mounted into Teflon flow-through diffusion cells; diffusion cells rinsed continuously with receptor fluid (0.9% sodium chloride in aqua bidest containing antibiotics); test substance applied for 8 h (no occlusion) and washed with shampoo; receptor fluid analyzed for zinc content at 0, 2, 4, 6, 8, 16, 24, 40, 48, 64, and 72 h using atomic absorption spectroscopy (10 ng/ml detection limit); skin samples and rinsing fluid also evaluated for zinc content	Study authors reported 0.3% zinc in receptor fluid, 1.3% zinc in horny layer, 0% zinc in residual skin for a total of 1.6% potentially absorbed zinc from applied concentration; percentages reflect correction for background zinc levels in skin and receptor fluid (levels not provided); total zinc recovery in experiment between 82.0% to 109.6% of applied amount	[31]
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	[88]
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%	[89]

Table 8. Dermal Penetration Studies

Test Substance(s)	Species	Sample Type or Test Population	Dose/Concentration	Procedure	Results	Reference
Zinc Sulfate, Zinc Undecylenate (each labeled with 131 µCi/mole ^{65}Zn)	Rabbit	n=2	2.5 mg Zinc Sulfate or 2.5 mg Zinc Undecylenate (vehicle=glycerin: propylene glycol, 1:1)	Test substance applied to 1 inch diameter circular regions of shaved back skin of 2 animals; skin sites on left side of back treated with 1 application and sites on right side treated with 2 applications made 24 h apart; treated sites excised and assayed for ^{65}Zn	By 6 h after single application of radiolabeled Zinc Sulfate 65% of applied radioactivity detected and by 24 h 19% of applied radioactivity detected; by 6 h after single application of radiolabeled Zinc Undecylenate 37% of applied radioactivity detected and by 24 h 23% detected; by 6 h after double application of radiolabeled Zinc Sulfate 3% of applied radioactivity detected and by 24 h 12% detected; by 6 h after double application of radiolabeled Zinc Undecylenate 6% of applied radioactivity detected and by 24 h 8% detected; radioautographic analysis detected ^{65}Zn in high concentrations 6 h after double applications of radiolabeled Zinc Undecylenate in cuticular and cortical regions of hair shaft and subdermal muscle; detection of ^{65}Zn low in dermis and epidermis; radioautographic analysis detected ^{65}Zn near areas stained to locate sulfhydryl and disulfide groups in hair shaft cortex and hair papilla; sulfhydryl and disulfide reactions with ^{65}Zn also noted in epidermis; study researchers suggested ^{65}Zn diffusion through hair follicles facilitated uptake of ^{65}Zn in skin	[58]

PBS = Phosphate Buffered Saline; TEWL = transepidermal water loss

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]

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

Test Substance(s)	Species/ Strain	Test Population	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Zinc Chloride (^{65}Zn radiolabeled, 0.5-1.1 mCi/ml)	Rat/ Sprague-Dawley	n=6-7 animals/group	1.1 or 125 µg zinc/ml supplied as Zinc Chloride at pH 1	25 µl of test substance applied to shaved 3 cm^2 skin area on both sides of back and occlusively covered; blood samples collected from tails at various intervals post-application; animals killed 2 h post-application; autoradiography performed on skin samples	Small and slightly higher ^{65}Zn activity observed with 1.1 µg/ml than 125 µg/ml concentration in serum and coagulum at 0.5 h and 2 h; percent of absorbed ^{65}Zn activity in skin 6.1% (1.1 µg/ml) and 3.6% (125 µg/ml); ^{65}Zn activity detected in dermis (near hair follicles), panniculus carnosus, and epidermis	90
				Oral		
Zinc Acetate (dihydrate)	Dog/ Beagle	n=6	0, 2, 4 mg/kg/day	3 consecutive phases of study conducted; each phase consisted of adaptation to diet for first week and urine and feces collection throughout second week; during phase 1 no additional supplementation of test substance to regular diet; in phase 2, 2 mg/kg/day test substance supplementation added to regular diet; in phase 3, 4 mg/kg/day test substance supplementation added to regular diet; regular diet contained 180 mg/kg zinc; blood samples collected prior to and after each phase	Mean fecal zinc levels: 693 µg/kg (control), 1325 µg/kg (2 mg/kg/day), 1641 µg/kg (4 mg/kg/day); mean urine zinc levels: 686 µg/kg (control), 1319 µg/kg (2 mg/kg/day), 1729 µg/kg (4 mg/kg/day); mean apparent absorption levels: 0.35 (control), 0.21 (2 mg/kg/day), 0.30 (4 mg/kg/day); mean zinc concentrations in blood: 74 µg/dl (control), 97 µg/dl (2 mg/kg/day), 116 µg/dl (4 mg/kg/day); digestion of crude protein, crude fiber, and crude fat unaffected by treatment	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

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

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 µg/h/dL (intragastric pH ≤ 3) and 378 µg/h/dL (intragastric pH ≥ 5)	24
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 (no further details)	63
Zinc Sulfate (heptahydrate)	Rat/ Wistar	n = 5/sex	2000 mg/kg	Test substance applied semi-occlusively for 24 h using GLP in accordance with OECD TG 402 (Acute Dermal Toxicity); animals observed for 15 days post-application	LD_{50} > 2000 mg/kg; erythema (grades 1-2 of max grade 4) and scabs (scales 1-2 of max scale 3) in treated skin reported on days 2-8	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; LD_{50} of 2460 mg/kg reported for Zinc Acetate (dihydrate)	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)	Single dosage administered using GLP in accordance with OECD TG 401 (Acute Oral Toxicity); controls not used; animals observed for 14 days post-administration and then killed and examined	LD_{50} > 500 mg/kg and < 2000 mg/kg; 3 males and 5 females died 3 days following dosing with 2000 mg/kg; all animals in 500 mg/kg group survived; clinical signs reported were sluggishness, blepharospasm, piloerection, soiled fur; gross pathology exam revealed no treatment-related changes	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 reported; no mortality or observed toxicity	22
Zinc Ricinoleate	Rat/ Wistar	n=5/sex/dosage	2000 mg/kg (water vehicle)	Animals dosed using GLP in accordance with OECD TG 401; animals observed 14 days post-dosing; animals killed after 14 days and examined; no controls used	LD_{50} > 2000 mg/kg reported; no toxicity or mortality observed; body weight gain normal; no treatment-related macroscopic observations during necropsy	26
Zinc Stearate	Rat	n=Not specified	Not specified	Procedures not provided	LD_{50} > 5000 mg/kg	63

Table 10. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
			Inhalation			
Zinc Chloride	Rat/ Sprague-Dawley	n=3 females/ group	600, 940, 1220, or 1950 mg Zn/m^3, supplied as Zinc Chloride (water vehicle)	Animals exposed to aerosol with MMAD of 2.3 µm for 10 min; animals observed for 7 days post-administration; necropsy performed	LC_{50} of 2000 mg/m^3 Zinc Chloride (952 mg Zn/m^3) reported; no animals died in 600 mg/m^3 group; 2 animals 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); 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) and 1% (15.8 mg/m^3)	Anesthetized animals exposed to 0.1% aerosol (MMAD ~0.1 µm) for 7.5 min; lung volume and function measured prior to experiment and 5, 15, 30, 60, 120, 180 min post-exposure; animals then exposed to 1% submicron aerosol for 7.5 min; lung volume and function measured 5, 15, and 30 min post-exposure	Total respiratory resistance, static lung compliance, functional residual capacity, specific total respiratory conductance, and specific lung compliance not substantially affected by 0.1% and 1% treatment	[96]
Zinc Sulfate	Dog	n=5	0.5% (8.3 mg/m^3)	Anesthetized animals exposed to aerosol (MMAD ~0.1 µm) for 4 h; lung volume and function measured prior to experiment and each hour during and for 2 hours after exposure	Total respiratory resistance, functional residual capacity, static lung compliance, specific lung compliance, specific total respiratory conductance, mean pulmonary arterial and carotid arterial pressures, cardiac output, heart rate, stroke volume, arterial pH, and arterial O_2 and CO_2 tensions not substantially affected by treatment	[96]
Zinc Sulfate	Sheep	n=6	0.1% (1.8 mg/m^3)	Conscious animals exposed to aerosol (MMAD ~0.1 µm) for 20 min; tracheal mucous velocity measured at baseline and 30, 60, 120, and 180 min from beginning of exposure period	Tracheal mucous velocity not substantially affected by treatment	[96]
Zinc Sulfate	Sheep	n=5	0.5% (8.3 mg/m^3)	Conscious animals exposed to aerosol (MMAD ~0.1 µm) for 4 h; tracheal mucous velocity measured prior to and at end of experiment then again 2 h post-exposure	Tracheal mucous velocity not substantially affected by treatment	[96]

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

Table 11. Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
				ANIMAL			
				Oral			
Zinc Acetate (dihydrate)	Rat/ Sprague-Dawley	n=10 females/ group	0, 160, 320, 640 mg/kg/day (sugar added to water vehicle for palatability)	3 mos	Animals dosed daily in drinking water in accordance with OECD TG 408 (Repeated Dose 90-Day Oral Toxicity in Rodents); negative controls received vehicle only	NOEL of 160 mg/kg/day for Zinc Acetate reported; 2 animals at 640 mg/kg/day level died; drinking water ingested and volume of urine excreted in 640 mg/kg/day group were lower than other treatment groups; food consumption, weight gain, feces excretion, and organ weights were unaffected by treatment at all dosage rates; hematocrit and hemoglobin levels unaffected by treatment; plasma urea and creatinine levels statistically significantly higher in 640 mg/kg/day group compared to controls; concentrations of zinc statistically significantly higher in liver, kidneys, heart, bone, and blood in 320 and 640 mg/kg/day groups compared to controls; zinc concentration in spleen statistically significantly higher compared to controls; severe histological lesions observed in kidneys in 640 mg/kg/day group	24,97
Zinc Sulfate (heptahydrate) (99.9% pure)	Mouse/ ICR and Rat/ Wistar	n=12 mice/sex/dosage; n=12 rats/sex/dosage	0, 300, 3000, 30,000 ppm	13 wks	Animals dosed daily in diet in accordance with OECD TG 408; negative controls used	<u>*Mouse results*</u>: NOEL of 3000 ppm (~458 mg/kg/day in males, ~479 mg/kg/day in females) reported; 4 animals died in 30,000 ppm group (33.3% mortality in males, 8.3% mortality in females); The following effects noted with 30,000 ppm treatment: depressed motility; histological analysis showed urinary tract impairment and exocrine gland regressive changes in pancreas; smaller body size; reduction in food intake during week 1 compared to controls; lower food efficiency compared to controls; decreased water consumption during week 1 which reversed in males but not in females; lower hematocrit and hemoglobin levels compared to controls; lower leukocyte level in males; morphological alterations in erythrocyte anisocytosis; polychroomatophilia and poikilocytosis in 6 males and 4 females with fore-stomach ulcers; decrease in total protein, glucose, and cholesterol and increase in alkaline phosphatase and urea nitrogen; abnormal liver enzyme levels; emaciation, ischemic discoloration of thyroid and kidney; pancreatic atrophy; thickening of small intestine; slight splenomegaly; relative and absolute organ weight fluctuations, but unclear if related to treatment; lesions in pancreas, intestine, stomach, spleen, kidney attributable to treatment; No treatment-related toxicity at ≤ 3000 ppm; slight, but reversible reduction in weight gain in females (300 ppm) after 1 week <u>*Rat results*</u>: NOEL of 3000 ppm; animals in groups fed ≤ 3000 ppm displayed no signs of treatment-related effects; 2 females (control and 3000 ppm group) killed because of suppurative pyelitis; no deaths in 30,000 ppm group; reduced weight gain in males and slightly reduced weight gain in females (30,000 ppm); smaller body size (in males at 30,000 ppm); at 30,000 ppm reduction in food intake during week 3 (in males) and weeks 1-6 (in females); slight reduction in food efficiency and water intake at 30,000 ppm (males only); reduction in leukocyte count (30,000 ppm) and in males slight decrease in hematocrit and hemoglobin; females showed slight increase in hemoglobin (3000 ppm); reduced liver enzymes, reduced protein, cholesterol, and calcium (in males at 30,000ppm); reduced calcium (in females at 3000 ppm and 30,000 ppm); relative and	21,98

Table 11. Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
						absolute organ weight fluctuations, but unclear if treatment-related; treatment-related pancreatic lesions observed (30,000 ppm)	
				Inhalation			
Zinc Sulfate (heptahydrate)	Rat/ Wistar Kyoto	n=12/group	Filtered air or 10, 30, or 100 µg/m^3 water soluble Zinc Sulfate (particle size 30-43 nm)	16 wks	Test substance administered through nose inhalation for 5 h/day for 3 days/wk; necropsy performed 48 h following final exposure; analysis of plasma/serum, cardiac RNA and cardiac mitochondria isolation, pathology of lung and heart, and broncho-alveolar lavage fluid analysis performed	Neutrophil and macrophage count, lavageable cells, and enzyme activity in bronchoalveolar lavage fluid not substantially changed by treatment; reduction in cytosolic glutathione peroxidase activity and succinate dehydrogenase activity and increase in levels of mitochondrial ferritin in heart; cell signaling genes revealed small changes (100 µg/m^3) detected in gene array analysis test; plasma/serum markers unaffected bytreatment; pathology revealed no pulmonary or cardiac changes as a result of treatment	[93]

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

Table 12. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Zinc Acetate	Mouse/ BALB/c	n= 30/group (sex distribution not specified)	500 or 1000 mg/l (water vehicle)	Test substance administered in drinking water beginning from day of mating through gestation, lactation, and post-weaning; vehicle controls used; humoral immunity test performed (mice injected with 0.5 ml of 15% sheep erythrocytes and killed after 5 days, spleen extracted and assayed for IgM and IgG producing cells); specific cell-mediated immunity test performed to examine mitogen-induced proliferation	LOAEL of 136 mg/kg/day zinc reported for male and female mice because mice exposed in utero continuing postnatally showed direct plaque-forming activity of spleen cells increase as did lymphocyte proliferation with mitogen stimulation; no clinical signs, mortality, body weight changes, food consumption, or gross pathological findings related to treatment observed; treatment-related hematological and clinical biochemistry findings observed, but no further details provided	[24]
Zinc Chloride (99.99% purity)	Rat/ Sprague-Dawley	n=25/sex/group	0, 7.5, 15, 30 mg/kg/day (water vehicle)	Test substance administered daily by gavage in accordance with OECD TG 416 (Two-Generation Reproduction Toxicity Study); animals dosed for 77 days before cohabitation, during cohabitation (21 days), and during gestation (21 days) and lactation (21 days) in females; controls dosed with vehicle only	F1 generation overall NOAEL of 7.5 mg/kg/day reported; parental animals from F0 and F1 generations showed reduced fertility and viability; reduced body weight of F1 and F2 pups in 30 mg/kg/day group, however no effects on weaning index, sex ratio, or litter size observed; F0 and F1 parental males and postpartum dams (F0 and F1) showed reduced body weight; reduced weights of brain, liver, kidney, spleen and seminal vesicles in F0 males and reduced weight of spleen and uterus of F0 females; reduced weights of brain, liver, kidney, adrenal, spleen, prostate and seminal vesicles of F1 males and reduced spleen and uterus of F1 females; no change in clinical signs or	[25,101]

Table 12. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
					clinical pathology in F0 and F1 parental rats, but alkaline phosphatase levels increased for F0 and F1 males and females; parental rats in both generations showed gross lesions in gastro-intestinal tract, lymphoreticular/hematopoietic and reproductive tract; F1 parental rats had reduced body fat; F1 male mortality rate of 0, 12, 8, and 4% and F1 female mortality rate of 0, 8, 12, and 20% reported for control, 7.5, 15, and 30 mg/kg/day groups, respectively	
Zinc Chloride (99.99% pure)	Rat/ Sprague-Dawley	n=25/group	0, 7.5, 15, 30 mg/kg/day (water vehicle)	Test substance administered daily by gavage; males and females dosed for 84 days through premating and mating (14 days), and during gestation (21 days) and lactation (21 days) in females; controls dosed with vehicle only	Difficulty in handling was main clinical sign reported at all treatment levels; implantation efficiency statistically significantly reduced in 7.5 mg/kg/day treated females; statistically significant increase in stillbirths (15 and 30 mg/kg/day); statistically significant decrease in pups per litter in all treated groups compared to controls; dose-dependent increase in birth mortality in treated animals; in treated (all levels) males statistically significant reduction in food consumption at varying time-points compared to controls; female body weight unaffected by treatment during premating phase, but males had statistically significant reduction in body weight (15 and 30 mg/kg/day groups) compared to controls in premating period; treated females showed statistically significant reduction in body weight during mating (30 mg/kg/day), gestation (15 and 30 mg/kg/day), and lactation (all treatment levels); statistically significant reduction in feed consumption (various treatment levels) during pregnancy and last week of lactation; food conversion ratio statistically significantly lower during pregnancy (all treatment levels), but unaffected during lactation; in treated females (various levels) relative weight ratios of kidney, pancreas, liver, brain, and uterus statistically significantly higher; in treated males (various levels) relative weight ratios of brain, liver, and testes statistically significantly increased while weight ratio of seminal vesicles and kidney statistically significantly decreased; no histopathological lesions found in treated males or females; in treated males and females (various levels) serum clinical chemistry parameters statistically significantly different than controls; white blood cell counts statistically significantly increased in treated females (15 and 30 mg/kg/day); male pups born to treated females (30 mg/kg/day) exhibited statistically significantly longer anogenital distance (female pups unaffected); male and female pups born to treated	[100]

Table 12. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
					females (various levels) showed statistically significantly earlier incisor eruption and eye opening versus controls	
Zinc Sulfate	Rat/ Wistar	n=25/group	0, 0.4, 2.0, 9.1, 42.5 mg/kg (water vehicle)	Pregnant, female rats dosed by gavage on days 6-15 of gestation; necropsy performed day 20; positive and negative controls used; skeletal and soft tissue examinations of fetuses performed	Maternal and developmental NOEL of 42.5 mg/kg (~17 mg/kg zinc equivalent) reported; no treatment-related effects observed	[102]
Zinc Sulfate	Rabbit/ Dutch	n=14-19/group	0, 0.6, 2.8, 13.0, 60.0 mg/kg (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 (~24 mg/kg zinc equivalent) reported; no treatment-related effects observed; positive controls performed as expected	[102]
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	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) comparted to control (12 conceptions out of 12 mated females) animals; lower number of implantation sites per pregnant female in treated (5) compared to controls (7), but not statistically significant; resorption sites in controls (2) similar to treated (1) animals; mean placental and fetal weights unaffected by treatment; no stillbirths or malformed fetuses Test 2: no statistically significant difference in number of conceptions in controls (10 out of 11 mated females conceived) compared to treated animals (14 out of 15 mated females conceived); no difference of implantation sites per pregnant female in controls compared to treated animals; resorption sites in controls (4) similar to treated (6) animals; mean placental and fetal weights unaffected by treatment; no stillbirths or	[104]

Table 12. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
					malformed fetuses	
Zinc Sulfate	Mouse/CD-1	n=25-30 animals/ group	0.3, 1.4, 6.5, and 30 mg/kg/day (30 mg/kg/day group equivalent to 12 mg or 6.8 mg Zn^{2+}/kg for anhydrate or heptahydrate, respectively)	Females dosed by gavage on days 6-15 of gestation; controls used; females killed on day 17 of gestation	Maternal and fetal NOAEL of 30 mg/kg/day reported; maternal body weight, maternal survival, number of corpora lutea, implantations and resorptions unaffected by treatment; live litters, fetus weights, fetus deaths, and sex ratio unaffected by treatment; no difference in soft or skeletal tissue abnormalities between treated and control groups	[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

Table 13. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
			IN VITRO		
Zinc Acetate	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100	50 to 7200 µg/plate	Ames test conducted with and without metabolic activation	Negative	[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 without metabolic activation; 4.2, 5.6, 7.5, 10, 13, 18, 24, 32, 42 µg/ml with metabolic activation	Mouse lymphoma assay (TK+/-) performed with and without metabolic activation; negative and positive controls used	Positive (dose-dependent) results both with and without metabolic activation; at 10 µg/ml, both with and without metabolic activation, mutation frequency doubled; controls performed as expected	[105]
Zinc Acetate	Chinese hamster ovary cells	25, 34, 45 µg/ml without metabolic activation; 45, 60, 80 µg/ml with metabolic activation	Chromosomal aberrations assay performed both with and without metabolic activation	Positive (dose-dependent) responses both with and without metabolic activation; controls performed as expected	[105]
Zinc Acetate	Rat hepatocytes	10 to 1000 µg/ml	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	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]

Table 13. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Zinc Acetate, Zinc Chloride, Zinc Sulfate	Human leukocytes	1.5 x 10^{-3}, 3.0 x 10^{-4}, 3.0 x 10^{-5}M zinc supplied as Zinc Acetate, Zinc Chloride, Zinc Sulfate (distilled water vehicle for Zinc Chloride and Zinc Sulfate; dimethyl sulfoxide vehicle for Zinc Acetate)	Clastogenicity experiment performed in separate cultures for each test substance or vehicle controls; inoculation occurred at 0 and 24 h; cultures harvested 48 and 72 h following initiation; cultures prepared for evaluation of chromosomal aberrations	Highest concentrations lethal for all three test substances; 3.0 x 10^{-4} and 3.0 x 10^{-5}M concentrations showed statistically significant increase in chromosomal aberrations compared to controls for all test substances; generally chromosomal aberrations higher in 72 h cultures for all test substances	[61]
Zinc Chloride	*S. typhimurium* TA98, TA100	1, 10, 25, 100 mg/l with metabolic activation 1, 10, 25 mg/l without metabolic activation (100 mg/l cytotoxic without metabolic activation) (water vehicle)	Ames test performed with and without metabolic activation as indicated; positive and negative controls used	Non-mutagenic; controls performed as expected	[107]
Zinc Chloride	*S. typhimurium* TA97	0, 15.62, 31.25, 62.50, 125, 250.5, 500, 1000 µM/plate for preincubation tests without inhibitor; 18.75, 37.5, 75, 150, 300 µM/plate for preincubation tests with inhibitor; 0, 75, 150, 200, 300 µM/plate for tests using individual Vogel Bonner minimal medium salts (vehicle=distilled, deionized water)	Ames test conducted; various preincubation mixtures were evaluated including water (distilled, deionized), sodium phosphate buffer (0.1 M, pH 7), or HEPES buffer in sodium and potassium chloride (0.1 M, pH 7); solvent controls used; in preincubation tests 500 µl water or buffer, 50 µl test substance, and 100 µl cell culture added to tubes and incubated at 37 °C for 30 min; then top agar added to tubes, mixed, and plated on agar plates; 44 to 48 h after incubation His^+ colonies scored; another set of tests using inhibitor diethyldithiocarbamate (chelator) were conducted; 50 µl inhibitor was added to preincubation test tube mixture following addition of cell culture and assayed similarly as above; agar contained Vogel Bonner minimal medium with salts including $MgSO_4$, $NaNH_4HPO_4$,K_2HPO_4, and citrate (pH 4.5); tests conducted to evaluate effect of individual salts' ability to inhibit mutagenesis of test substance; salt component (controls without salt also used) added after cell culture and assayed similarly as above; HEPES buffer system used	Zinc mutagenic in the distilled, deionized water or HEPES buffer systems used in preincubation test conditions; at 1000 µM/plate in the HEPES buffer system toxicity noted as no microcolonies observed; no mutagenesis attributed to zinc observed in phosphate buffer system; diethyldithiocarbamate inhibited mutagenesis of zinc; all 4 salts tested inhibited mutagenesis of zinc to some extent compared to mutagenicity of zinc observed in controls with no salt added	[181]
Zinc Chloride	*Escherichia coli* WP2	3.2 mM	Experiment conducted to determine if test substance caused DNA damage and induced a pleiotropic response in *E. coli*; test substance exposure was 20 h; vehicle, negative, and positive controls used	Test substance caused 2-fold increase in λ prophage induction compared to controls; controls performed as expected	[25]
Zinc Chloride	Mouse L5178Y/$TK^{+/-}$ lymphoma cells	1.21 to 12.13 µg/ml in normal saline followed by filter sterilization	Cells were directly exposed to test substance for 3 h in L5178Y $TK^{+/-}$ to $TK^{-/-}$ point-mutation assay; solvent controls used	Non-mutagenic; test substance did not induce trifluorothymidine-resistant mutants	[108]
Zinc Chloride (99.9% pure)	Human dental pulp cells (D824 cells)	30, 100, 300 µM	Chromosomal aberrations assay performed without metabolic activation; cells treated for 3 or 30 h; negative controls used; an additional experiment performed using same concentrations of treated cells with metabolic activation (negative controls and positive controls used)	Treated cells, both with and without metabolic activation, negative for chromosomal aberrations; controls performed as expected	[82]

Table 13. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Zinc Chloride	Human peripheral blood lymphocytes	1, 10, 100 mg/l (water vehicle)	Micronucleus assay conducted; cell proliferation kinetics (mitotic index) test also performed; negative controls used for both experiments	Genotoxicity observed at 100 mg/l in micronucleus assay (micronuclei statistically significantly higher than negative controls); cytotoxicity noted at 100 mg/l; micronuclei counts higher than negative control at 1 and 10 mg/l, but not statistically significant; controls performed as expected; mitotic activity decreased with increasing concentration (statistically significant at 100 mg/l after 48 h exposure compared to controls); cytotoxicity noted at 100 mg/l	107
Zinc Chloride	Human peripheral blood leukocytes	1.5×10^{-3}, 3.0×10^{-4}, 3.0×10^{-5}M zinc supplied as Zinc Chloride	Clastogenicity experiment performed; inoculation occurred at 0 and 24 h; cultures harvested 48 and 72 h following initiation; cultures prepared for evaluation of mitotic index and chromosomal aberrations; distilled water controls used	Study researchers found excess zinc to be clastogenic and mitostatic (1.5×10^{-3}M lethal at 48 and 72 h); statistically significant increase in chromosomal aberrations at 48 and 72 h with both 0 and 24 h inoculation periods for 3.0×10^{-4} and 3.0×10^{-5}M compared to controls; statistically significant decrease in mitotic index value at 48 and 72 h with both 0 and 24 h inoculation periods for 3.0×10^{-4} and 3.0×10^{-5}M compared to controls	109
Zinc Chloride	Human leukocytes	1.5×10^{-4} and 3.0×10^{-4}M zinc supplied as Zinc Chloride (deionized water vehicle)	Cytokinesis-block micronucleus assay performed to determine if test substances induced micronucleus formation; each test substance added to separate cell cultures 24 h following initiation; at 72 h cultures terminated; positive and vehicle controls used	Statistically significant increase in micronucleated cytokinesis- blocked cells in treated (both concentrations, however, not dose-dependent) compared to vehicle control cells	110
Zinc Chloride	Human lymphocyte cultures	0, 0.003M, 0.0003M or 0.00003M	0.003M used to evaluate cytotoxicity; 0.0003M or 0.00003M test substance added to 48-h (first cell division) and 72-h (second cell division) cultures of human lymphocytes from healthy donor at time zero and 24 h following initiation; negative controls used; metaphases from cultures assayed for aberrations (numerical and structural); 100 cells analyzed for each treatment or control group	Mitotic activity inhibited at 0.003M; Control results (48 h culture): 3 aneuploid cells, 0 cells in endoreduplication, 1 gap chromatid aberrations; 0.0003M results at time zero (48 h culture): 1 aneuploid cells, 0 cells in endoreduplication, 2 gap chromatid aberrations; 0.0003M results at 24 h post-initiation (48 h culture): 4 aneuploid cells, 0 cells in endoreduplication, 2 gap chromatid aberrations, 2 fragment chromosome aberrations; 0.00003M results at time zero (48 h culture): 4 aneuploid cells, 0 cells in endoreduplication, 3 gap chromatid aberrations, 1 dicentric chromosome aberrations; 0.00003M results at 24 h post-initiation (48 h culture): 4 aneuploid cells, 2 gap chromatid aberrations, 2 fragment chromosome aberrations; Control results (72 h culture): 2 aneuploid cells, 0 cells in endoreduplication, 3 gap chromatid aberrations; 0.0003M results at time zero (72 h culture): 3 aneuploid cells, 0 cells in endoreduplication, 0 structural aberrations; 0.0003M results at 24 h post-initiation (72 h culture): 6 aneuploid cells, 0 cells in endoreduplication, 3 gap chromatid aberrations, 1 fragment chromosome aberrations; 0.00003M at time zero (72 h culture): 4 aneuploid cells, 0 cells in endoreduplication, 3 gap chromatid aberrations, 2	180

Table 13. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
				dicentric chromosome aberrations 0.00003M at 24 h post-initiation (72 h culture): 2 aneuploid cells, 1 cell in endoreduplication, 2 gap chromatid aberrations, 1gap chromosome aberrations	
Zinc Nitrate (hexahydrate)	*S.typhimurium* TA98, TA100	0.01 mM and 1 mM	Ames test performed with and without metabolic activation (S9 mix)	Negative	111
Zinc Stearate	*S.typhimurium* TA1535, TA1537, TA98, TA100; *Saccharomyces cerevisiae* strain 04	Range of test concentrations used based on 50% survival value, however concentrations used not specified (dimethylsulfoxide, water, or saline vehicles)	A bacterial reverse mutation assay was performed with and without metabolic activation; water, saline, and positive controls used	Non-mutagenic	27
Zinc Sulfate	*S. typhimurium* TA1535, TA1537, TA98, TA100, TA1538	5 concentrations up to 3600 µg/plate (no further details provided)	Ames test conducted both with and without metabolic activation; solvent and negative controls not used; positive controls used	Non-mutagenic; positive controls performed as expected	21
Zinc Sulfate	*S. cerevisiae* diploid strain D4	5000/ 1000 ppm (vehicle 0.1 M potassium phosphate buffer, pH 7.5)	Mitotic recombination assay performed with 4-h exposure duration; gene conversion evaluated at ade2 and trp5 loci; solvent controls used	Non-convertogenic	28
			IN VIVO		
Zinc Chloride	Mouse/ C57B1; n=25/group	0.5% zinc supplied as Zinc Chloride	For 1 month animals fed standard diet, which included 1.1% calcium, or diet low in calcium (0.03%); test substance was added to each type of diet; controls were administered a normal or low-calcium diet without test substance; at study termination 10 animals killed for assay	Statistically significant decrease in body weight for treated animals on either the standard or low-calcium diet compared to their respective controls; treated animals on standard diet had statistically significantly lower serum calcium than controls on standard diet; treated animals on low-calcium diet had statistically significant increase in chromosomal aberrations compared to controls on low-calcium diet	182
Zinc Chloride	Mouse/ Swiss albino; n = 5/group	7.5, 10, 15 mg/kg	Single dosage administered intraperitoneally; mice killed 24 h post-administration; negative and positive controls used; control animals killed 24 h post-administration	Statistically significant, dose dependent increase in chromosomal aberrations of bone-marrow cells in treatment (at all levels tested) compared to control animals	112
Zinc Chloride	Mouse/ Swiss albino; n = 5/group	7.5, 10, 15 mg/kg	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	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

Table 13. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Zinc Sulfate	Mouse/ Swiss albino, n=6 males/group	0, 5.7, 8.55, 11.40, 14.25, 17.10, 19.95 mg/kg (distilled water vehicle)	Animals orally dosed; Comet assay performed (alkaline single cell gel electrophoresis) to detect single strand DNA breaks (damaged DNA resembles a comet and normal DNA resembles a halo); blood samples collected 24, 48, 72, 96 h and during first week following treatment; negative (distilled water) and positive (25 mg/kg cyclophosphamide administered intraperitoneally) controls used; DNA damaged quantified by comment tail-length	Statistically significant dose-dependent DNA damage seen in treated compared to control animals; DNA damage gradually decreased (comet tail-length decreased) at 48 h and beyond for each dosage level; DNA comet tail-length in all treated groups similar to controls by 1 week post-treatment; cell viability confirmed at each dosage level and time point; no treatment-related deaths reported	[113]

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

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 ≥ 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 5th treatment day animals killed Rabbit tests: Test 1-0.5 ml of each test substance or control (groups 1-6) applied to skin sites on either side of mid-dorsal line (6 treatment sites per rabbit) for 5 consecutive days in open patch test (animals restrained while treatment dried); 24 h after 5th treatment day animals killed Test 2-0.5 ml of each test substance or control (groups 1-6) applied to sterile gauze and secured to skin sites on either side of mid-dorsal line (6 treatment sites per rabbit) with occlusive covering for 3 days; 3 days post-application coverings removed to examine skin and 2 animals killed; treatment re-applied as above to 2 remaining animals for 2 more days and then coverings removed to examine skin and animals killed Guinea Pig test: test substance or controls applied to skin sites (1 test substance group or control group in 3 replicates per animal) for 5 consecutive days in open patch test (animals restrained while treatment dried); 24 h after 5th treatment day animals killed Histology (all animals) and epidermal cell kinetics (mouse only) performed	Zinc 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]

Table 14. Dermal Irritation and Sensitization Studies

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 5cm^2 shaved skin for 5 consecutive days in open patch test; skin treated with vehicle only on other side of mid-dorsal line served as control; skin observed during and after test period; animals killed on day 6 *Occlusive patch test performed*: 0.5 ml test substance applied to 5 x 5 cm^2 shaved skin and covered with occlusive patch for 3 days; patch removed and skin examined 3 days post-application and 2 animals killed; test substance re-applied to remaining animals and occlusively covered for 2 more days, then those animals were killed; skin from test animals evaluated for histology	Severely irritating in both open and occlusive patch tests; no reactions in controls; epidermal hyperplasia with ulceration and parakeratosis seen in open patch test, which were also noted in occlusive patch test, but more severely; study authors indicated zinc highly bound to epidermal keratin	[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 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 6cm^2 shaved, intact skin area and covered semi-occlusively for 4 h using GLP in accordance with OECD TG 404; animals examined 1, 24, 48, and 72 h post-application; untreated skin used as control	Non-irritating; no skin reactions observed	[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 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 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]

Table 14. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Test Population-	Concentration (Vehicle)	Procedure	Results	Reference
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
Zinc Undecylenate	Human	n=10	0.25% in a foot powder	A single application of 0.0212 g 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 dodecylsulfate)	Maximization test performed in accordance with OECD TG 406 (no further details provided)	After first challenge treatment, weak reactions reported in 5 of 10 treated animals and 2 of 5 control animals; following second challenge, reactions noted in 4 of 10 treated animals and 2 of 5 controls	63
Human						
Zinc Chloride	Human	n=55	0.327% in a foundation, tested at 70% in squalene (test concentration 0.229% % Zinc Chloride)	HRIPT; 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)	HRIPT; 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	HRIPT; 20 mg applied neat using Finn chambers with a 50 mm^2 inner surface	Not an irritant or sensitizer	126
Zinc Myristate	hman		20% in a powder product (tested at 70% in squalene) (test concentration 14% Zinc Myristate)	HRIPT; 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; HRIPT = Human Repeat Insult Patch Test; LLNA = Local Lymph Node Assay; non-GLP = non-Good Laboratory Practice; OECD TG = Organization for Economic Co-operation and Development Test Guideline

Table 15. Ocular Irritation

Test Substance(s)	Species/ Strain	Sample Type or Test Population	Concentration (Vehicle)	Procedure	Results	Reference
IN VITRO						
Zinc Acetate (97%)	Chicken	n=3 eyeballs/group	0.03 g (no vehicle)	Enucleated eyeballs incubated for 45-60 min at 32 °C with physiological saline prior to treatment; test substance applied to corneas for 10 seconds followed by 20 ml saline rinse; method followed GLP in accordance with OECD TG 438 (Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants); observations made 30, 75, 180, and 240 min post-treatment rinse; negative and positive controls used	Defects and partial lesion (of anterior epithelium) in treated corneas reported; Bowman's membrane showed separating layers in treated corneas; study author's reported irreversible effects on eye causing eye corrosion/irritation; controls performed as expected	[24]
Zinc Citrate	N/A	Human corneal tissue (three-dimensional model)	Particulate powder (no vehicle)	50.4 mg test substance applied to tissue for 6 h using GLP in accordance with OECD TG 492 (Reconstructed Human Cornea-like Epithelium Test Method for Identifying Chemicals Not Requiring Classification and Labelling for Eye Irritation or Serious Eye Damage); negative and positive controls used	Test substance considered eye irritant; relative absorbance values of 4.7% reported (threshold for eye irritation potential ≤ 60%)	[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 instilled into lower right formix of conjunctiva using GLP in accordance with OECD TG 405; eyes unrinsed following application of test substance; untreated eye used as control; animals observed 7 days post-application	Very irritating; conjunctival damage not completely reversible by 7 days in all 3 animals; severe corneal lesions not completely reversible in 2 animals by 7 days; iris congestion and chemosis not fully reversible in 2 animals by 7 days	[25]
Zinc Nitrate (hexahydrate)	Rabbit	n=?	Concentration not specified	Procedures not provided	Irritating; study author's reported dimness of cornea, mucous membrane ulceration, and cicadricial alterations in eyelids	[32]
Zinc Phosphate	Rabbit/ New Zealand White	n=3	100 mg (no vehicle)	Test substance instilled into conjunctival sac of left eye using GLP in accordance with OECD TG 405; other eye served as untreated control; eyes (unrinsed) examined at 1, 24, 48, and 72 h post-application	Non-irritating; in 2 animals slight irritation of conjuctivae and chemosis noted within 48 h post-application; no iris or corneal lesions or conjunctival discharge observed	[22]
Zinc Ricinoleate	Rabbit/ New Zealand White	n=6	White powder (no vehicle)	0.1 g test substance instilled into conjunctival sac of left eye (right eye used as control) using GLP in accordance with OECD TG 405; eyes (unrinsed) examined at 1, 24, 48, and 72 h post-application	Non-irritating; slight-to-moderate conjunctival irritation observed in all animals 1 and 24 h post-application, but reversed in all animals by 48 h; iris and cornea unaffected by treatment	[26]

Test Substance(s)	Species/ Strain	Sample Type or Test Population	Concentration (Vehicle)	Procedure	Results	Reference
Zinc Sulfate	Rabbit/ New Zealand White	n=3 males	Unchanged (no vehicle)	~ 98.1 mg test substance instilled into conjunctival sac of eye (untreated eye used as control) in accordance with OECD TG 405; eyes (unrinsed) observed 1, 24, 48, and 72 h and 7, 14, and 21 days post-treatment	Severely irritating; corneal injury in 2 rabbits reversed by 24 to 72 h; conjunctival irritation (redness), chemosis and discharge seen in all animals; lower eyelid tissue, nictitating membrane, and/or sclera showed yellow/white spots from day 7 through study termination; study authors considered spots (containing unknown encapsulated material causing protrusions) to be indicative of necrosis; 1 animal showed reduced eyelid elasticity at 72 h and 7 days post-treatment	[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	Test substance administered daily on average beginning week 25 of gestation; study was blind, randomized; controls did not receive treatment	Less pregnancy and labor maternal and fetal complications observed in treated subjects compared to controls; occurrence of large-for-date and small-for-date infants reduced in treated subjects compared to controls; no treatment-related adverse effects reported; study authors report zinc is transferred from mother to fetus through placenta	[130]
Zinc Citrate	n=13 pregnant women in treatment group; n= 16 pregnant women in control group; treatment and control patients above were compliant	100 mg Zinc Citrate equivalent to 22.5 mg zinc	Test substance or placebo administered daily during last 15 to 25 weeks of gestation; when iron/folate supplements prescribed by patient's doctor they were taken 12 h apart from test substance or placebo; criteria for trial (treatment group): subjects who smoked and this was first time pregnancy or previous small for gestational age baby; criteria for trial (control group): subjects who smoked and this was first time pregnancy or previous small for gestational age baby; low pregnancy weight	Induction of labor and intrauterine growth retardation statistically significantly lower in treatment group compared to controls; Caesarean section, placental weight, birthweight, and Ponderal index (ratio of height to weight) in treatment group not statistically different from controls; mean hemoglobin levels similar between groups; side effects attributed by patients to be from treatment included nausea and heartburn; side effects from placebo tablet reported to be aftertaste, diarrhea, lethargy, and nausea	[131]
Zinc Sulfate	n=179 pregnant women between 16 and 20 week gestation completed study (n=89 treatment group; n=90 placebo group); 196 recruited, but 6 refused participation and 11subjects excluded due to < 70% compliance during study	50 mg elemental zinc supplied as Zinc Sulfate	Randomized, double-blind study conducted; women received either test substance or placebo daily (mid-morning); 1 mg folic acid and 30 mg ferrous sulfate were also administered (at night); 20 weeks duration of supplementation in treatment and placebo groups	Average birth weight higher in treated group (3513 ± 400 g) compared to placebo (3352 ± 544) group; treatment showed no effect on neonatal head circumference and length, gestational age, or maternal complications; 2 placebo group subjects (2.2%) had infants born with intrauterine growth retardation (birth weight < 10^{th} percentile), but this did not occur in treatment group; placebo group only had 2.2% subjects with pregnancy-induced hypertension; 2 subjects in each group had stillborn fetuses or an infant death soon after birth; preterm deliveries occurred in treatment (9 subjects) and in placebo (7 subjects) groups; premature infants in treatment group were > 2500 g except 1 infant who died at 28 weeks gestation; no low birth weight occurred in treatment group, but 6 infants born in placebo group had low birth weights	[132]
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	[133]

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557346	ZINC ACETATE	09B - Mouthwashes and Breath Fresheners	2
36393201	ZINC ASPARTATE	03G - Other Eye Makeup Preparations	1
36393201	ZINC ASPARTATE	05A - Hair Conditioner	1
36393201	ZINC ASPARTATE	05F - Shampoos (non-coloring)	12
36393201	ZINC ASPARTATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	3
36393201	ZINC ASPARTATE	10A - Bath Soaps and Detergents	1
36393201	ZINC ASPARTATE	12A - Cleansing	2
36393201	ZINC ASPARTATE	12D - Body and Hand (exc shave)	2
36393201	ZINC ASPARTATE	12F - Moisturizing	2
36393201	ZINC ASPARTATE	12H - Paste Masks (mud packs)	1
3486359	ZINC CARBONATE	03G - Other Eye Makeup Preparations	1
3486359	ZINC CARBONATE	12C - Face and Neck (exc shave)	1
7646857	ZINC CHLORIDE	03B - Eyeliner	1
7646857	ZINC CHLORIDE	03C - Eye Shadow	7
7646857	ZINC CHLORIDE	04E - Other Fragrance Preparation	1
7646857	ZINC CHLORIDE	05A - Hair Conditioner	1
7646857	ZINC CHLORIDE	05F - Shampoos (non-coloring)	1
7646857	ZINC CHLORIDE	05I - Other Hair Preparations	1
7646857	ZINC CHLORIDE	07A - Blushers (all types)	1
7646857	ZINC CHLORIDE	07C - Foundations	3
7646857	ZINC CHLORIDE	07G - Rouges	30
7646857	ZINC CHLORIDE	07I - Other Makeup Preparations	2
7646857	ZINC CHLORIDE	09A - Dentifrices	4
7646857	ZINC CHLORIDE	09B - Mouthwashes and Breath Fresheners	3
7646857	ZINC CHLORIDE	09C - Other Oral Hygiene Products	2
7646857	ZINC CHLORIDE	12A - Cleansing	1
7646857	ZINC CHLORIDE	12C - Face and Neck (exc shave)	3
7646857	ZINC CHLORIDE	12F - Moisturizing	9
7646857	ZINC CHLORIDE	12G - Night	1
7646857	ZINC CHLORIDE	12H - Paste Masks (mud packs)	2
7646857	ZINC CHLORIDE	12I - Skin Fresheners	2
7646857	ZINC CHLORIDE	12J - Other Skin Care Preps	1
546463	ZINC CITRATE	07I - Other Makeup Preparations	1
546463	ZINC CITRATE	09A - Dentifrices	7
546463	ZINC CITRATE	09C - Other Oral Hygiene Products	1
546463	ZINC CITRATE	10B - Deodorants (underarm)	3
546463	ZINC CITRATE	11A - Aftershave Lotion	1
4468024	ZINC GLUCONATE	02A - Bath Oils, Tablets, and Salts	1
4468024	ZINC GLUCONATE	02B - Bubble Baths	1
4468024	ZINC GLUCONATE	03B - Eyeliner	15
4468024	ZINC GLUCONATE	03D - Eye Lotion	7
4468024	ZINC GLUCONATE	03E - Eye Makeup Remover	1
4468024	ZINC GLUCONATE	03G - Other Eye Makeup Preparations	12

4468024	ZINC GLUCONATE	05A - Hair Conditioner	1
4468024	ZINC GLUCONATE	05E - Rinses (non-coloring)	2
4468024	ZINC GLUCONATE	05F - Shampoos (non-coloring)	7
4468024	ZINC GLUCONATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	5
4468024	ZINC GLUCONATE	05I - Other Hair Preparations	7
4468024	ZINC GLUCONATE	06A - Hair Dyes and Colors (all types requiring caution state	4
4468024	ZINC GLUCONATE	07C - Foundations	8
4468024	ZINC GLUCONATE	07E - Lipstick	10
4468024	ZINC GLUCONATE	07F - Makeup Bases	1
4468024	ZINC GLUCONATE	10A - Bath Soaps and Detergents	3
4468024	ZINC GLUCONATE	10B - Deodorants (underarm)	14
4468024	ZINC GLUCONATE	10E - Other Personal Cleanliness Products	4
4468024	ZINC GLUCONATE	11A - Aftershave Lotion	5
4468024	ZINC GLUCONATE	11G - Other Shaving Preparation Products	2
4468024	ZINC GLUCONATE	12A - Cleansing	32
4468024	ZINC GLUCONATE	12C - Face and Neck (exc shave)	58
4468024	ZINC GLUCONATE	12D - Body and Hand (exc shave)	7
4468024	ZINC GLUCONATE	12F - Moisturizing	49
4468024	ZINC GLUCONATE	12G - Night	14
4468024	ZINC GLUCONATE	12H - Paste Masks (mud packs)	17
4468024	ZINC GLUCONATE	12I - Skin Fresheners	7
4468024	ZINC GLUCONATE	12J - Other Skin Care Preps	23
4468024	ZINC GLUCONATE	13B - Indoor Tanning Preparations	1
20427581	ZINC HYDROXIDE	12D - Body and Hand (exc shave)	1
20427581	ZINC HYDROXIDE	12F - Moisturizing	1
16039535	ZINC LACTATE	09B - Mouthwashes and Breath Fresheners	1
2452019	ZINC LAURATE	02B - Bubble Baths	1
2452019	ZINC LAURATE	03A - Eyebrow Pencil	1
2452019	ZINC LAURATE	03B - Eyeliner	1
2452019	ZINC LAURATE	03C - Eye Shadow	54
2452019	ZINC LAURATE	05F - Shampoos (non-coloring)	10
2452019	ZINC LAURATE	07A - Blushers (all types)	5
2452019	ZINC LAURATE	07B - Face Powders	8
2452019	ZINC LAURATE	07C - Foundations	22
2452019	ZINC LAURATE	07G - Rouges	3
2452019	ZINC LAURATE	07I - Other Makeup Preparations	1
2452019	ZINC LAURATE	10A - Bath Soaps and Detergents	3
2452019	ZINC LAURATE	10E - Other Personal Cleanliness Products	1
2452019	ZINC LAURATE	12A - Cleansing	3
2452019	ZINC LAURATE	12D - Body and Hand (exc shave)	2
16260278	ZINC MYRISTATE	03B - Eyeliner	1
16260278	ZINC MYRISTATE	03C - Eye Shadow	19
16260278	ZINC MYRISTATE	03G - Other Eye Makeup Preparations	5
16260278	ZINC MYRISTATE	07A - Blushers (all types)	15
16260278	ZINC MYRISTATE	07B - Face Powders	18

16260278	ZINC MYRISTATE	07C - Foundations	1
13040192	ZINC RICINOLEATE	07E - Lipstick	2
13040192	ZINC RICINOLEATE	08G - Other Manicuring Preparations	1
13040192	ZINC RICINOLEATE	10B - Deodorants (underarm)	21
13040192	ZINC RICINOLEATE	10C - Douches	1
13040192	ZINC RICINOLEATE	12A - Cleansing	1
13040192	ZINC RICINOLEATE	12F - Moisturizing	1
557051	ZINC STEARATE	01B - Baby Lotions, Oils, Powders, and Creams	1
557051	ZINC STEARATE	02B - Bubble Baths	2
557051	ZINC STEARATE	03A - Eyebrow Pencil	19
557051	ZINC STEARATE	03B - Eyeliner	44
557051	ZINC STEARATE	03C - Eye Shadow	1309
557051	ZINC STEARATE	03F - Mascara	2
557051	ZINC STEARATE	03G - Other Eye Makeup Preparations	23
557051	ZINC STEARATE	04C - Powders (dusting and talcum, excluding aftershave tal	28
557051	ZINC STEARATE	06H - Other Hair Coloring Preparation	6
557051	ZINC STEARATE	07A - Blushers (all types)	318
557051	ZINC STEARATE	07B - Face Powders	428
557051	ZINC STEARATE	07C - Foundations	73
557051	ZINC STEARATE	07D - Leg and Body Paints	2
557051	ZINC STEARATE	07E - Lipstick	5
557051	ZINC STEARATE	07F - Makeup Bases	4
557051	ZINC STEARATE	07G - Rouges	6
557051	ZINC STEARATE	07H - Makeup Fixatives	4
557051	ZINC STEARATE	07I - Other Makeup Preparations	26
557051	ZINC STEARATE	12A - Cleansing	1
557051	ZINC STEARATE	12C - Face and Neck (exc shave)	6
557051	ZINC STEARATE	12D - Body and Hand (exc shave)	1
557051	ZINC STEARATE	12E - Foot Powders and Sprays	1
557051	ZINC STEARATE	12F - Moisturizing	4
557051	ZINC STEARATE	12G - Night	1
557051	ZINC STEARATE	12J - Other Skin Care Preps	2
557051	ZINC STEARATE	13B - Indoor Tanning Preparations	3
557051	ZINC STEARATE	13C - Other Suntan Preparations	2
7446200	ZINC SULFATE	03C - Eye Shadow	8
7446200	ZINC SULFATE	03D - Eye Lotion	2
7446200	ZINC SULFATE	03G - Other Eye Makeup Preparations	1
7446200	ZINC SULFATE	05A - Hair Conditioner	13
7446200	ZINC SULFATE	05F - Shampoos (non-coloring)	14
7446200	ZINC SULFATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
7446200	ZINC SULFATE	05I - Other Hair Preparations	3
7446200	ZINC SULFATE	07A - Blushers (all types)	6
7446200	ZINC SULFATE	07B - Face Powders	5
7446200	ZINC SULFATE	07C - Foundations	7

7446200	ZINC SULFATE	07E - Lipstick	1
7446200	ZINC SULFATE	10A - Bath Soaps and Detergents	12
7446200	ZINC SULFATE	11G - Other Shaving Preparation Products	2
7446200	ZINC SULFATE	12A - Cleansing	15
7446200	ZINC SULFATE	12C - Face and Neck (exc shave)	17
7446200	ZINC SULFATE	12D - Body and Hand (exc shave)	2
7446200	ZINC SULFATE	12F - Moisturizing	11
7446200	ZINC SULFATE	12G - Night	2
7446200	ZINC SULFATE	12H - Paste Masks (mud packs)	2
7446200	ZINC SULFATE	12J - Other Skin Care Preps	8
7733020	ZINC SULFATE, ANHYDROUS	05F - Shampoos (non-coloring)	1
7733020	ZINC SULFATE, ANHYDROUS	12C - Face and Neck (exc shave)	1
1314983	ZINC SULFIDE	07E - Lipstick	3
1314983	ZINC SULFIDE	07I - Other Makeup Preparations	3
1314983	ZINC SULFIDE	08E - Nail Polish and Enamel	4

Concentration of Use by FDA Product Category – Zinc Compounds*

(zinc molecular weight 63.38 molecular/formula weights stated below if ingredient used in lipstick and/or oral care products)

Zinc Gluconate (MW 210.5)
Zinc Acetate
Zinc Ascorbate
Zinc Aspartate
Zinc Carbonate
Zinc Carbonate Hydroxide
Zinc Chloride (MW 136.31)
Zinc Chloride Hydroxide
Zinc Citrate (MW 574.43)
Zinc Cysteinate
Zinc Glutamate
Zinc Glycinate
Zinc Hexametaphosphate
Zinc Hydroxide
Zinc Lactate (MW 243.52)
Zinc Laurate
Zinc Myristate
Zinc Neodecanoate
Zinc Nitrate
Zinc Palmitate
Zinc Phosphate (MW 386.17)
Zinc Ricinoleate (MW 660.3)
Zinc Salicylate
Zinc Stearate (MW 632.3)
Zinc Sulfate
Zinc Sulfide
Zinc Undecylenate

Ingredient	**Product Category**	**Maximum Concentration of Use**
Zinc Gluconate	Other bath preparations	0.000005%
Zinc Gluconate	Eyeliners	0.047-0.5%
Zinc Gluconate	Eye shadows	0.0095-3%
Zinc Gluconate	Eye lotions	0.0048-0.019%
Zinc Gluconate	Hair conditioners	0.00005-0.0003%
Zinc Gluconate	Shampoos (noncoloring)	0.00024-0.5%
Zinc Gluconate	Tonics, dressings and other hair grooming aids Not spray	0.00024% 0.003%
Zinc Gluconate	Blushers	0.51%
Zinc Gluconate	Foundations	0.001-0.075%
Zinc Gluconate	Lipstick	0.1% (0.031% Zn)
Zinc Gluconate	Makeup bases	0.0095%
Zinc Gluconate	Other makeup preparations	0.5%
Zinc Gluconate	Aftershave lotions	0.0024%
Zinc Gluconate	Skin cleansing (cleansing lotions, liquids and pads)	0.00048-0.5%
Zinc Gluconate	Face and neck products Not spray	 0.024-1%
Zinc Gluconate	Body and hand products Not spray	 0.001-0.05%
Zinc Gluconate	Moisturizing products Not spray	 0.00048-0.001%
Zinc Gluconate	Paste masks and mud packs	0.01-0.048%
Zinc Gluconate	Other skin care preparations	0.001-0.24%
Zinc Gluconate	Suntan products Not spray	 0.001%
Zinc Gluconate	Other suntan preparations	0.001%
Zinc Ascorbate	Baby shampoos	0.01%

Zinc Ascorbate	Eyeliners	0.047%
Zinc Ascorbate	Colognes and toilet waters	0.05%
Zinc Ascorbate	Hair conditioners	5%
Zinc Ascorbate	Shampoos (noncoloring)	0.01%
Zinc Ascorbate	Face powders	0.095%
Zinc Ascorbate	Bath soaps and detergents	0.05%
Zinc Ascorbate	Deodorants Not spray	0.3%
Zinc Ascorbate	Face and neck products Not spray	0.1%
Zinc Ascorbate	Body and hand products Not spray	0.05%
Zinc Ascorbate	Suntan products Not spray	0.05%
Zinc Carbonate	Shampoos (noncoloring)	1.6%
Zinc Chloride	Eyeliners	0.064%
Zinc Chloride	Eye shadows	0.039%
Zinc Chloride	Hair conditioners	0.000095-0.11%
Zinc Chloride	Shampoos (noncoloring)	0.00095-0.21%
Zinc Chloride	Tonics, dressings and other hair grooming aids	0.003%
Zinc Chloride	Other hair preparations (noncoloring)	0.0001%
Zinc Chloride	Blushers	0.024%
Zinc Chloride	Face powders	0.04-0.47%
Zinc Chloride	Foundations	0.002-0.33%
Zinc Chloride	Rouges	0.0016%
Zinc Chloride	Mouthwashes and breath fresheners	0.088% (0.041% Zn)
Zinc Chloride	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.091%
Zinc Chloride	Face and neck products Not spray or powder	0.00075%
Zinc Citrate	Dentifrices	2% (0.22% Zn)
Zinc Citrate	Mouthwashes and breath fresheners	0.28% (0.031% Zn)
Zinc Citrate	Bath soaps and detergents	0.05%
Zinc Glycinate	Foundations	0.009%
Zinc Lactate	Dentifrices	0.44% (0.12% Zn)
Zinc Lactate	Mouthwashes and breath fresheners	0.25% (0.065% Zn)
Zinc Lactate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1.8%
Zinc Laurate	Face powders	3-7%
Zinc Laurate	Foundations	1-5%
Zinc Laurate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1.2%
Zinc Myristate	Eyebrow pencils	5-7%
Zinc Myristate	Eyeliners	0.51-5%
Zinc Myristate	Eye shadows	3-20%
Zinc Myristate	Powders (dusting and talcum)	3-5%

Zinc Myristate	Blushers	0.6-8%
Zinc Myristate	Face powders	2-20%
Zinc Myristate	Foundations	1-6%
Zinc Myristate	Lipstick	0.063-5% (0.0077-0.61% Zn)
Zinc Myristate	Makeup bases	5%
Zinc Myristate	Nail polish and enamel	0.035%
Zinc Myristate	Other manicuring preparations	0.005%
Zinc Myristate	Face and neck products Not spray	 5%
Zinc Myristate	Body and hand products Not spray	 15%
Zinc Phosphate	Dentifrices	1% (0.17% Zn)
Zinc Ricinoleate	Lipstick	1.1% (0.11% Zn)
Zinc Ricinoleate	Deodorants Not spray Aerosol Pump spray	 0.82-2% 2.3% 0.82%
Zinc Ricinoleate	Face and neck products Not spray	 0.15%
Zinc Salicylate	Deodorants Not spray	 0.47%
Zinc Stearate	Eyebrow pencils	4-12%
Zinc Stearate	Eyeliners	1-15%
Zinc Stearate	Eye shadows	1.5-32%
Zinc Stearate	Eye lotions	1%
Zinc Stearate	Mascara	3%
Zinc Stearate	Other eye makeup preparations	3-6%
Zinc Stearate	Perfumes	0.3%
Zinc Stearate	Powders (dusting and talcum)	1.1-5%
Zinc Stearate	Other hair coloring preparations	3.3%
Zinc Stearate	Blushers	0.75-11.2%
Zinc Stearate	Face powders	1.8-14%
Zinc Stearate	Foundations	1-7%
Zinc Stearate	Leg and body paints	2%
Zinc Stearate	Lipstick	0.5% (0.05% Zn)
Zinc Stearate	Makeup bases	5%
Zinc Stearate	Makeup fixatives	1-3.9%
Zinc Stearate	Other makeup preparations	3.9-11%
Zinc Stearate	Dentifrices	2% (0.2% Zn)
Zinc Stearate	Other shaving preparations	0.28%
Zinc Stearate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.39%
Zinc Stearate	Face and neck products Not spray	 0.2-1%
Zinc Stearate	Body and hand products	

	Not spray or powder	0.5%
Zinc Stearate	Moisturizing products Not spray	4%
Zinc Stearate	Night products Not spray	4%
Zinc Sulfate	Eye shadows	0.02%
Zinc Sulfate	Shampoos (noncoloring)	0.15%
Zinc Sulfate	Tonics, dressings and other hair grooming aids	0.003%
Zinc Sulfate	Blushers	0.022%
Zinc Sulfate	Face powders	0.02%
Zinc Sulfate	Foundations	0.005-0.025%
Zinc Sulfate	Nail polish and enamel	0.0001-0.001%
Zinc Sulfate	Bath soaps and detergents	0.0003-0.057%
Zinc Sulfate	Deodorants Not spray	0.0015%
Zinc Sulfate	Skin cleansing (cold cream, cleansing lotions, liquids and pads)	0.0025%
Zinc Sulfate	Face and neck products Not spray	0.0008-0.12%
Zinc Sulfate	Body and hand products Not spray	0.07-0.1%
Zinc Sulfate	Moisturizing products Not spray	1%
Zinc Sulfate	Paste masks and mud packs	0.002%
Zinc Sulfide	Nail polish and enamel	6.6%
Zinc Undecylenate	Foot powders and sprays	0.25%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2016

Table prepared: December 14, 2016;

December 7, 2017 added Zinc concentrations for lipstick and oral care products

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: December 5, 2017

SUBJECT: Zinc Laurate, Zinc Myristate and Zinc Chloride

EVIC Portugal. 2007. Summary: Human repeat insult patch test with challenge (blush formula containing 7% Zinc Laurate).

Anonymous. 2011. Clinical safety evaluation repeated insult patch test of a powder product containing 20% Zinc Myristate (tested at 70% in squalene).

Anonymous. 2015. Clinical safety evaluation repeated insult patch test of a face powder containing 0.465% Zinc Chloride (tested at 70% in squalene).

Anonymous. 2011. Clinical safety evaluation repeated insult patch test of a foundation containing 0.327% Zinc Chloride (tested at 70% in squalene).

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

EVIC portugal

Study / Product References :

Coordinator Centre : Pm 197 / 06-3001

Investigator Centre : Pm 197 / 115.06M

[redacted]: [redacted]

HUMAN REPEAT INSULT PATCH TEST WITH CHALLENGE

[redacted]

TEST PRODUCT : BLUSH FORMULA [redacted]

Contains 7% Zinc Laurate

Study report

[redacted] **January 25th 2007**

30 pages in this report including 23 in Appendices

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HUMAN REPEAT INSULT PATCH TEST WITH CHALLENGE

TABLE OF CONTENTS

I . AIM OF THE STUDY

This study intended to confirm that the application of several cosmetic products including the product **BLUSH FORMULA** [redacted] to volunteer subjects, under maximised conditions, according to the "modified Marzulli and Maibach" method, did not cause delayed contact allergic responses.

II . ETHICS

The test project was submitted to the previous agreement of the internal committee of Evic France (coordinator centre) before its performance (opinion n° 816/06 of December 1st, 2006).

III . COORDINATOR AND INVESTIGATOR CENTRES AND TECHNICAL STAFF

III.1 . Coordinator centre

[redacted]

III.2 . Investigator centre

Evic Portugal Lda
Rua Leitão de 8arros 7A
1S00 - 383 Lisboa
PORTUGAL
tel : 00 351 21 778 13 24
00 351 21 778 18 75

III.3 . Technical staff

Investigator : Doctor Leonor GIRÃO, MD (Dermatologist)

Responsible technician : Pedro CONTREIRAS PINTO, MSc

IV . DATES OF PERFORMANCE OF THE STUDY

8eginning on: December 1st, 2006

End on: January 12th, 2007

V . PROTOCOL

The study was performed according to [redacted] **reference RCL-SEC-01/E (June 2002) and to the specific dispositions** relating to the test products and the study, supplied by the sponsor.

Modifications from the protocol concerning the experimental conditions of application were decided by the investigator (due to Christmas holiday) in accordance with the sponsor and are the following ones: the study started on December 1st, 2006 instead of December 4th, 2006 which induced some modifications of the D-dates of controls as follows:

- induction phase : 3 consecutive weeks

  * application of the product to a perfectly delimited site, under patch on D1, D4, D6, D8, D11, D13, D15, D18, D20.

  * patch removal
    - D6, D8, D13, D15, D20, D22.
    - after 72 h of contact on D4, D11, D18.

  * controls : skin examination and questioning (paragraph IX.6) before patching on D1, and about 15 minutes (or more, if redness appeared after removal of the adhesive), after patch removal on D4, D6, D8, D11, D13, D15, D18, D20, D22.

- Rest period : 2 consecutive weeks at least (4 weeks at the most).

  * no application of product.

- challenge : 1 week.

  * application of the product to a perfectly delimited virgin site and to the site defined for the induction phase, under patch on D39.

  * patch removal after 48 h of contact on D41.

  * controls : skin examination and questioning (paragraph VIII.6) before patching on D39 and about 15 minutes (or more, if redness appeared after removal of the adhesive), after patch removal on D41 and D43 (48 and 96 h after application).

These modifications have no impact on the validity of the study results.

VI . TEST PRODUCTS

VI.1 . Total number of products simultaneously tested in the study

The total number of tested products was 12.

This report concerns only the product BLUSH FORMULA[redacted]

VI.2 . Identification of the test product

Denomination	BLUSH
Reference	[redacted]
Batch number	06 11 07
Evic France / Evic Portugal reference	06-3001 / 115.06M
Galenic form and organoleptic characteristics	Pink powder
Number and type of samples	4 plastic pots
Content of the samples	250 g

VI.3 . Experimental conditions of application of the test product

Patch material*	Experimental conditions of use	Quantity applied
Finn Chamber standard® : aluminium cupula in which the product was put down, kept in position by an hypoallergenic adhesive : Scanpor® (inner diameter: 8 mm, surface : 50 mm²)	As it is	20 mg

* if reactions application of a semi-occlusive patch (TruMed® : absorbent support in Webril® on which the product was put down (160 µl), kept in position by a non woven medical adhesive (surface : 400 mm²))

VI.4 . Information concerning the product

The documents relating to the test product supplied with the samples were the qualitative formula and the Sponsor's letter of agreement particularly concerning the conformity of the formula to the regulations in force and its safety.

VII . VOLUNTEERS

VII.1 . Number

The number of volunteers whose data had to be exploitable at the end of the study was 100.

106 volunteers were included in the study.

Two volunteers (ref. 10 and 89) discontinued for personal reasons independent of the test product and no exclusion was decided by the investigator.

The compatibility of the test product was therefore assessed in 104 volunteers.

The confirmation of the absence of allergenic potential of the test product was assessed in 104 volunteers.

VII.2 . Inclusion and non inclusion criteria

All the volunteers corresponded to the specific inclusion and non inclusion criteria defined in the protocol.

Their typological characteristics are defined in **Appendices 1/1 to 1/6.**

VIII . RESULTS

The individual data of the skin examination and questioning of the volunteers are enclosed in **Appendices 2/1 to 2/8 and 3/1 to 3/8.**

In brief :

Induction phase			
Category of reaction	**Type of reactivity on the induction site**	**Number and percentage of reactive volunteers according to the category of reaction**	**Number and percentage of reactive volunteers for all the categories of reaction**
E : Erythema	None	0 / 0%	0 / 0%
A : ICDRG scale	None	0 / 0%	
M : Complementary mention	None	0 / 0%	

Challenge			
Category of reaction	**Type of reactivity on the induction site and/ or the virgin site**	**Number and percentage of reactive volunteers according to the category of reaction**	**Number and percentage of reactive volunteers for all the categories of reaction**
E : Erythema	None	0 / 0%	0 / 0%
A : ICDRG scale	None	0 / 0%	
M : Complementary mention	None	0 / 0%	

IX. CONCLUSION

Under the experimental conditions adopted, the repeated applications of the product **BLUSH FORMULA** [redacted], under occlusive patch, on a panel of 104 volunteers, induced no reaction of irritation and the product **has a very good skin compatibility.**

Moreover, the repeated applications induced **no allergic reaction.**

Signatures and dates

Investigator : Doctor Leonor GIRÃO (Dermatologist)

I the undersigned, Leonor GIRÃO, declare that the overall conduct of the study was carried out under my responsibility having in mind the basic principles of Good Clinical Practices ("Avis aux promoteurs et aux investigateurs pour les essais cliniques des médicaments" : principes généraux – FR.OB – 1987, international recommendations ICH E 6, step 4, of 1/5/1996 and general principals of the Portuguese law 46/2004 from August 19th).

26/2/07

Quality Manager : Nuno FURTADO

I the undersigned, Nuno FURTADO, declare that:
- the final report was examined on January 30th, 2007,
- the results reported accurately and completely reflect the raw data of the study.

26.2.2007

[redacted]

FINAL REPORT

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

Face powder containing 0.465% Zinc Chloride tested dissolved in squalene (70% product)

Tested concentration 0.326% Zinc Chloride

Sponsor

[redacted]

Sponsor Representatives

[redacted]

Clinical Testing Facility

[redacted]

Sponsor Code: [redacted]

Date of Final Report

7-30-15

[redacted]

[redacted]

SIGNATURE PAGE

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

[redacted]

7/29/15
Date

[redacted]

7/27
Date

[redacted]

7/31/15
Date

[redacted]

QUALITY ASSURANCE STATEMENT

This study ([redacted]) was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in 21 CFR Part 50 (Protection of Human Subjects – Informed Consent) and the Standard Operating Procedures of [redacted]

For purposes of this clinical study:

_X_	Informed Consent was obtained.
____	Informed Consent was not obtained.
_X_	An IRB review was not required.
____	An IRB review was conducted and approval to conduct the proposed clinical research was granted.

To assure compliance with the study protocol, the Quality Assurance Unit completed an audit of the applicable study records and report. This report is considered a true and accurate reflection of the testing methods and source data.

[redacted]

31 July 2015
Date

[redacted]

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

1.0 OBJECTIVE

The objective of this study was to determine the irritation and/or sensitization potential of the test article after repeated application under occlusive patch test conditions to the skin of human subjects (exclusive panel).

2.0 SPONSOR

[redacted]

2.1 Sponsor Representatives

[redacted]

3.0 CLINICAL TESTING FACILITY

The study was conducted by:

[redacted]

4.0 CLINICAL INVESTIGATORS

Study Director:
Principal Investigator:
Medical Investigator:

[redacted]

5.0 STUDY DATES

Study initiation: June 17, 2015

Final evaluation: July 24, 2015

[redacted]

6.0 ETHICS

6.1 Ethical Conduct of the Study

This study was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in Title 21 of the U.S. Code of Federal Regulations (CFR), the Declaration of Helsinki and/or [redacted] Standard Operating Procedures.

6.2 Subject Information and Consent

This study was conducted in compliance with CFR Title 21, Part 50 (Informed Consent of Human Subjects). Informed Consent was obtained from each subject in the study and documented in writing before participation in the study. A copy of the Informed Consent was provided to each subject.

7.0 TEST MATERIAL

The test article used in this study was provided by:

[redacted]

It was received on June 1, 2015 and identified as follows:

[redacted] Entry No.	Test Article ID	Description
[redacted]	[redacted]	[redacted]

*The test article was prepared at [redacted]% w/w in [redacted]

8.0 TEST SUBJECTS

Approximately 50 male or female subjects ranging in age from 18 to 79 years were to be empanelled for this test. Subject demographics are listed in Table 1.

The subjects chosen were to be dependable and able to read and understand instructions. The subjects were not to exhibit any physical or dermatological condition that would have precluded application of the test article or determination of potential effects of the test article.

[redacted]

9.0 TEST PROCEDURE

The 9 Repeated Insult (occlusive) Patch Test (9-RIPT)[1] was conducted as follows:

9.1 Induction Phase

A sufficient amount of the test article (approximately 0.1 g – 0.15 g) was placed onto a Parke-Davis Readi-Bandage® occlusive patch (approximately 25 - 38 mg/cm^2 of test material) and applied to the back of each subject between the scapulae and waist, adjacent to the spinal mid-line. This procedure was performed by a trained technician/examiner and repeated every Monday, Wednesday and Friday until 9 applications of the test article had been made.

The subjects were instructed to remove the patch 24 hours after application. Twenty-four hour rest periods followed the Tuesday and Thursday removals and 48-hour rest periods followed each Saturday removal. Subjects returned to the Testing Facility and the site was scored by a trained examiner just prior to the next patch application.

If a subject developed a positive reaction of a level 2 erythema or greater during the Induction phase or if, at the discretion of the Study Director, the skin response warranted a change in site, the patch was applied to a previously unpatched, adjacent site for the next application. If a level 2 reaction or greater occurred at the new site, no further applications were made. However, any reactive subjects were subsequently Challenge patch tested.

9.2 Challenge Phase

After a rest period of approximately 2 weeks (no applications of the test article), the Challenge patch was applied to a previously unpatched (virgin) test site. The site was scored 24 and 72 hours after application. All subjects were instructed to report any delayed skin reactivity that occurred after the final Challenge patch reading. When warranted, selected test subjects were called back to the Clinic for additional examinations and scoring to determine possible increases or decreases in Challenge patch reactivity.

Dermal responses for both the Induction and Challenge phases of the study were scored according to the following 6-point scale:

0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

All other observed dermal sequelae (eg, edema, dryness, hypo- or hyperpigmentation) were appropriately recorded on the data sheet and described as mild, moderate or severe.

---

[1] Marzulli FN, Maibach HI. (1976) Contact allergy: predictive testing in man. *Contact Dermatitis.* 2, 1-17.

[redacted]

9.0 TEST PROCEDURE (CONT'D)

9.3 Data Interpretation

Edema, vesicles, papules and/or erythema that persist or increase in intensity either during the Induction and/or Challenge phase may be indicative of allergic contact dermatitis. Allergic responses normally do not resolve or improve markedly at 72-96 hours.

Exceptions to typical skin reactions may occur. These may include, but not be limited to, symptoms of allergic contact sensitivity early in the Induction period to one or more test products. When this occurs in one subject, such a reaction usually suggests either an idiosyncratic response or that the subject had a pre-exposure/sensitization to the test material or component(s) of the test material or a cross-reactivity with a similar product/component. Data for such reactions will be included in the study report but will not be included in the final study analysis/conclusion of sensitization.

10.0 RESULTS AND DISCUSSION

(See Table 2 for Individual Scores)

A total of 55 subjects (11 males and 44 females ranging in age from 19 to 73 years) were empanelled for the testing procedure. Fifty-two (52/55) subjects satisfactorily completed the test procedure on Test Article: [redacted]. Three (3/55) subjects discontinued for personal reasons unrelated to the conduct of the study. Discontinued subject data are shown up to the point of discontinuation, but are not used in the Conclusions section of this final report.

Induction Phase Summary

Test Article	Induction Scores (Number of Responses)						Evidence of Irritation
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

Challenge Phase Summary

Test Article	Challenge Scores (Number of Responses)						Evidence of Sensitization
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

There was no skin reactivity observed at any time during the course of the study.

11.0 CONCLUSIONS

Under the conditions of a repeated insult (occlusive) patch test procedure conducted in 52 subjects, Test Article: [redacted] was "Dermatologist-Tested" and was not associated with skin irritation or allergic contact dermatitis in human subjects.

[redacted]

[redacted]

TABLE 1

SUBJECT DEMOGRAPHICS

Test Article: [redacted]

Subject No.	Initials	Age	Sex	Race	Subject No.	Initials	Age	Sex	Race
1	V-M	42	F	HS	29	FLM	37	F	HS
2	WLD	54	M	CA	30	L-I	57	F	CA
3	VLC	27	F	CA	31	CMB	24	F	CA
4	D-C	44	F	CA	32	R-B	48	F	CA
5	M-V	45	F	HS	33	A-D	49	F	BA
6	K-F	21	F	HS	34	M-C	44	F	HS
7	J-R	36	F	HS	35	T-D	23	F	CA
8	LGF	53	F	CA	36	D-B	44	F	CA
9	F-F	69	M	CA	37	RRM	65	M	CA
10	P-F	73	F	CA	38	P-F	54	F	CA
11	RMG	49	F	HS	39	PAR	69	F	CA
12	J-C	24	F	HS	40	RJM	60	F	CA
13	JDI	28	F	CA	41	NAB	20	F	CA
14	E-D	68	F	CA	42	J-P	34	F	HS
15	KRN	29	F	CA	43	D-S	55	F	CA
16	FPI	63	M	CA	44	D-B	57	F	CA
17	MKH	68	M	CA	45	G-D	60	F	HS
18	C-S	19	M	HS	46	S-G	42	F	HS
19	B-B	59	F	HS	47	P-N	29	M	HS
20	GSB	58	F	CA	48	C-L	36	F	CA
21	S-G	60	F	CA	49	J-S	39	F	HS
22	K-G	72	M	CA	50	R-S	44	M	HS
23	JLV	39	M	BH	51	F-G	36	M	CA
24	EJG	26	F	HS	52	E-M	53	F	HS
25	M-G	64	F	CA	53	M-W	64	F	CA
26	S-A	41	F	HS	54	KAL	19	F	CA
27	N-A	56	F	CA	55	SLA	42	F	HS
28	JLC	44	F	CA					

Shaded area = Discontinued subject

BA = Black/African-American
BH = Black Hispanic
CA = Caucasian
HS = Hispanic

[redacted]

TABLE 2

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST – OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	1	2	3	4	5	6	7	8	9	24hr	72hr
1	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	Discontinued							
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	Discontinued							
27	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0

Scale:0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

[redacted]

TABLE 2 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number 1	2	3	4	5	6	7	8	9	Challenge Virgin Site 24hr	72hr
31	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0
50	0	Discontinued									
51	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0

Scale:0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

[redacted]

FINAL REPORT

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

foundation containing 0.327% Zinc Chloride tested at 70% in Squalene - 0.229% Zinc Chloride tested

Sponsor

[redacted]

Sponsor Representatives

[redacted]

Clinical Testing Facility

[redacted]

Sponsor Code: [redacted]

[redacted]

Date of Final Report

4-25-11

[redacted]

[redacted]

SIGNATURE PAGE

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

[redacted]

4/28/11
Date

[redacted]

20 Apr 2011
Date

[redacted]

4/27/11
Date

[redacted]

QUALITY ASSURANCE STATEMENT

This study [redacted]) was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in 21 CFR Part 50 (Protection of Human Subjects – Informed Consent) and the Standard Operating Procedures of [redacted]

For purposes of this clinical study:

__X__ Informed Consent was obtained.

_____ Informed Consent was not obtained.

__X__ An IRB review was not required.

_____ An IRB review was conducted and approval to conduct the proposed clinical research was granted.

To assure compliance with the study protocol, the Quality Assurance Unit completed an audit of the applicable study records and report. This report is considered a true and accurate reflection of the testing methods and source data.

[redacted]

25 April 2011
Date

[redacted]

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

1.0 OBJECTIVE

The objective of this study was to determine the irritation and/or sensitization potential of the test article after repeated application under occlusive patch test conditions to the skin of human subjects (exclusive panel).

2.0 SPONSOR

[redacted]

2.1 Sponsor Representatives

[redacted]

3.0 CLINICAL TESTING FACILITY

The study was conducted by:

[redacted]

4.0 CLINICAL INVESTIGATORS

Study Director:
Principal Investigator:
Medical Investigator:

[redacted]

5.0 STUDY DATES

Study initiation: February 23, 2011

Final evaluation: April 1, 2011

[redacted]

6.0 ETHICS

6.1 Ethical Conduct of the Study

This study was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in Title 21 of the U.S. Code of Federal Regulations (CFR), the Declaration of Helsinki and/or [redacted] Standard Operating Procedures.

6.2 Subject Information and Consent

This study was conducted in compliance with CFR Title 21, Part 50 (Informed Consent of Human Subjects). Informed Consent was obtained from each subject in the study and documented in writing before participation in the study. A copy of the Informed Consent was provided to each subject.

7.0 TEST MATERIAL

The test article used in this study was provided by:

[redacted]

It was received on January 17, 2011 and identified as follows:

[redacted] Entry No.	Test Article I.D.	Description
[redacted]	[redacted]	[redacted]

*The test article was prepared at [redacted]% w/w in [redacted]) and was volatilized at least 30 minutes, but less than 90 minutes, on the patch prior to application to the skin.

8.0 TEST SUBJECTS

Approximately 50 male or female subjects ranging in age from 18 to 79 years were to be empanelled for this test. Subject demographics are listed in Table 1.

The subjects chosen were to be dependable and able to read and understand instructions. The subjects were not to exhibit any physical or dermatological condition that would have precluded application of the test article or determination of potential effects of the test article.

[redacted]

9.0 TEST PROCEDURE

The 9 Repeated Insult (occlusive) Patch Test (9-RIPT) was conducted as follows:

9.1 Induction Phase

A sufficient amount of the test article (an amount to adequately cover the surface of the patch unit – approximately 0.1 g – 0.15 g) was placed onto a Parke-Davis Readi-Bandage® occlusive patch, which was applied to the back of each subject between the scapulae and waist, adjacent to the spinal mid-line. This procedure was performed by a trained technician/examiner and repeated every Monday, Wednesday and Friday until 9 applications of the test article had been made.

The subjects were instructed to remove the patch 24 hours after application. Twenty-four hour rest periods followed the Tuesday and Thursday removals and 48-hour rest periods followed each Saturday removal. Subjects returned to the Testing Facility and the site was scored by a trained examiner just prior to the next patch application.

If a subject developed a positive reaction of a level 2 erythema or greater during the Induction phase or if, at the discretion of the Study Director, the skin response warranted a change in site, the patch was applied to a previously unpatched, adjacent site for the next application. If a level 2 reaction or greater occurred at the new site, no further applications were made. However, any reactive subjects were subsequently Challenge patch tested.

9.2 Challenge Phase

After a rest period of approximately 2 weeks (no applications of the test article), the Challenge patch was applied to a previously unpatched (virgin) test site. The site was scored 24 and 72 hours after application. All subjects were instructed to report any delayed skin reactivity that occurred after the final Challenge patch reading. When warranted, selected test subjects were called back to the Clinic for additional examinations and scoring to determine possible increases or decreases in Challenge patch reactivity.

Dermal responses for both the Induction and Challenge phases of the study were scored according to the following 6-point scale:

0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

All other observed dermal sequelae (eg, edema, dryness, hypo- or hyperpigmentation) were appropriately recorded on the data sheet and described as mild, moderate or severe.

[redacted]

[redacted]

9.0 TEST PROCEDURE (CONT'D)

9.3 Data Interpretation

Edema, vesicles, papules and/or erythema that persist or increase in intensity either during the Induction and/or Challenge phase may be indicative of allergic contact dermatitis. Allergic responses normally do not resolve or improve markedly at 72-96 hours.

Exceptions to typical skin reactions may occur. These may include, but not be limited to, symptoms of allergic contact sensitivity early in the Induction period to one or more test products. When this occurs in one subject, such a reaction usually suggests either an idiosyncratic response or that the subject had a pre-exposure/sensitization to the test material or component(s) of the test material or a cross-reactivity with a similar product/component. Data for such reactions will be included in the study report but will not be included in the final study analysis/conclusion of sensitization.

10.0 RESULTS AND DISCUSSION

(See Table 2 for Individual Scores)

A total of 56 subjects (5 males and 51 females ranging in age from 18 to 77 years) were empanelled for the testing procedure. Fifty-five (55/56) subjects satisfactorily completed the test procedure on Test Article: [redacted]. One (1/56) subject discontinued for personal reasons unrelated to the conduct of the study. Discontinued subject data are shown up to the point of discontinuation, but are not used in the Conclusions section of this final report.

Induction Phase Summary

Test Article	Induction Scores (Number of Responses)						Evidence of Irritation
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

Challenge Phase Summary

Test Article	Challenge Scores (Number of Responses)						Evidence of Sensitization
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

There was no skin reactivity observed at any time during the course of the study.

11.0 CONCLUSIONS

Under the conditions of a repeated insult (occlusive) patch test procedure conducted in 55 subjects, Test Article: [redacted] was "Dermatologist-Tested" and was not associated with skin irritation or allergic contact dermatitis in human subjects.

[redacted]

[redacted]

TABLE 1

SUBJECT DEMOGRAPHICS

Test Article: [redacted]

Subject No.	Initials	Age	Sex	Race	Subject No.	Initials	Age	Sex	Race
1	D-M	34	F	CA	29	L-P	52	F	HS
2	F-S	43	F	CA	30	C-D	53	F	CA
3	B-L	60	F	CA	31	A-C	46	F	HS
4	AMT	65	F	CA	32	S-B	59	F	CA
5	A-M	54	F	CA	33	D-L	44	F	BA
6	WLM	55	F	CA	34	TML	38	F	BA
7	JJS	34	M	HS	35	DRU	58	M	CA
8	MAQ	43	F	CA	36	MMD	63	F	CA
9	M-S	47	F	CA	37	BAS	55	F	CA
10	JLE	53	F	CA	38	B-V	52	F	CA
11	DMM	48	F	CA	39	LMK	63	F	CA
12	ALJ	50	F	CA	40	EAK	18	F	OT
13	ALP	38	F	CA	41	CEB	69	F	CA
14	EMG	57	F	CA	42	E-S	71	F	CA
15	D-D	55	F	CA	43	Y-C	69	F	CA
16	N-V	35	F	HS	44	A-L	56	F	OT
17	M-M	73	F	CA	45	CRD	53	F	CA
18	G-P	46	F	CA	46	TNH	27	F	BA
19	C-P	70	F	CA	47	ECC	27	F	BA
20	R-C	44	F	CA	48	SAS	47	F	CA
21	KFB	35	M	CA	49	M-R	48	F	CA
22	AMM	60	M	BA	50	ARV	21	F	CA
23	P-H	51	F	CA	51	J-H	52	F	BA
24	J-S	66	F	CA	52	JAH	56	F	BA
25	A-T	77	M	BA	53	PJA	70	F	CA
26	LKB	54	F	CA	54	R-V	41	F	CA
27	J-B	56	F	CA	55	GCL	69	F	CA
28	TTM	69	F	CA	56	TRH	41	F	BA

BA = Black/African American
CA = Caucasian
HS = Hispanic
OT= Other

Shaded area = Discontinued subject

[redacted]

[redacted]

TABLE 2

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST – OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	1	2	3	4	5	6	7	8	9	24hr	72hr
1	0	0	0	0	0	0	0	0	0	0	0
2	0	Discontinued									
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0

Scale: 0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechlae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

[redacted]

TABLE 2 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST – OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	1	2	3	4	5	6	7	8	9	24hr	72hr
31	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0

Scale:0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

[redacted]

FINAL REPORT

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

powder product containing 20% Zinc Myrista

Sponsor

[redacted]

tested at 70% in squalene (tested concentration 14% Zinc Myristate)

Sponsor Representatives

[redacted]

Clinical Testing Facility

[redacted]

Sponsor Code: [redacted]

Date of Final Report

8-12-11

[redacted]

[redacted]

SIGNATURE PAGE

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

[redacted]

11 Aug 2011
Date

[redacted]

10 Aug 2011
Date

[redacted]

8/10/11
Date

[redacted]

QUALITY ASSURANCE STATEMENT

This study ([redacted]) was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in 21 CFR Part 50 (Protection of Human Subjects – Informed Consent) and the Standard Operating Procedures of [redacted]

For purposes of this clinical study:

X	Informed Consent was obtained.
____	Informed Consent was not obtained.
X	An IRB review was not required.
____	An IRB review was conducted and approval to conduct the proposed clinical research was granted.

To assure compliance with the study protocol, the Quality Assurance Unit completed an audit of the applicable study records and report. This report is considered a true and accurate reflection of the testing methods and source data.

[redacted]

12 Aug 2011
Date

[redacted]

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

1.0 OBJECTIVE

The objective of this study was to determine the Irritation and/or sensitization potential of the test article after repeated application under occlusive patch test conditions to the skin of human subjects (exclusive panel).

2.0 SPONSOR

[redacted]

2.1 Sponsor Representatives

[redacted]

3.0 CLINICAL TESTING FACILITY

The study was conducted by:

[redacted]

4.0 CLINICAL INVESTIGATORS

Study Director:
Principal Investigator:
Medical Investigator:

[redacted]

5.0 STUDY DATES

Study initiation: June 29, 2011

Final evaluation: August 5, 2011

[redacted]

6.0 ETHICS

6.1 Ethical Conduct of the Study

This study was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in Title 21 of the U.S. Code of Federal Regulations (CFR), the Declaration of Helsinki and/or [redacted] Standard Operating Procedures.

6.2 Subject Information and Consent

This study was conducted in compliance with CFR Title 21, Part 50 (Informed Consent of Human Subjects). Informed Consent was obtained from each subject in the study and documented in writing before participation in the study. A copy of the Informed Consent was provided to each subject.

7.0 TEST MATERIAL

The test article used in this study was provided by:

[redacted]

It was received on June 13, 2011 and identified as follows:

[redacted] Entry No.	Test Article I.D.	Description
[redacted]	[redacted]	[redacted]

*The test article was prepared at [redacted]% w/w [redacted]

8.0 TEST SUBJECTS

Approximately 50 male or female subjects ranging in age from 18 to 79 years were to be empanelled for this test. Subject demographics are listed in Table 1.

The subjects chosen were to be dependable and able to read and understand instructions. The subjects were not to exhibit any physical or dermatological condition that would have precluded application of the test article or determination of potential effects of the test article.

[redacted]

9.0 TEST PROCEDURE

The 9 Repeated Insult (occlusive) Patch Test (9-RIPT)[1] was conducted as follows:

9.1 Induction Phase

A sufficient amount of the test article (approximately 0.1 g – 0.15 g) was placed onto a Parke-Davis Readi-Bandage® occlusive patch (approximately 25 - 38 mg/cm^2 of test material) and applied to the back of each subject between the scapulae and waist, adjacent to the spinal mid-line. This procedure was performed by a trained technician/examiner and repeated every Monday, Wednesday and Friday until 9 applications of the test article had been made.

The subjects were instructed to remove the patch 24 hours after application. Twenty-four hour rest periods followed the Tuesday and Thursday removals and 48-hour rest periods followed each Saturday removal. Subjects returned to the Testing Facility and the site was scored by a trained examiner just prior to the next patch application.

If a subject developed a positive reaction of a level 2 erythema or greater during the Induction phase or if, at the discretion of the Study Director, the skin response warranted a change in site, the patch was applied to a previously unpatched, adjacent site for the next application. If a level 2 reaction or greater occurred at the new site, no further applications were made. However, any reactive subjects were subsequently Challenge patch tested.

9.2 Challenge Phase

After a rest period of approximately 2 weeks (no applications of the test article), the Challenge patch was applied to a previously unpatched (virgin) test site. The site was scored 24 and 72 hours after application. All subjects were instructed to report any delayed skin reactivity that occurred after the final Challenge patch reading. When warranted, selected test subjects were called back to the Clinic for additional examinations and scoring to determine possible increases or decreases in Challenge patch reactivity.

Dermal responses for both the Induction and Challenge phases of the study were scored according to the following 6-point scale:

0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

All other observed dermal sequelae (eg, edema, dryness, hypo- or hyperpigmentation) were appropriately recorded on the data sheet and described as mild, moderate or severe.

---

[1] Marzulli FN, Maibach HI. (1976) Contact allergy: predictive testing in man. *Contact Dermatitis.* 2, 1-17.

[redacted]

[redacted]

9.0 TEST PROCEDURE (CONT'D)

9.3 Data Interpretation

Edema, vesicles, papules and/or erythema that persist or increase in intensity either during the Induction and/or Challenge phase may be indicative of allergic contact dermatitis. Allergic responses normally do not resolve or improve markedly at 72-96 hours.

Exceptions to typical skin reactions may occur. These may include, but not be limited to, symptoms of allergic contact sensitivity early in the Induction period to one or more test products. When this occurs in one subject, such a reaction usually suggests either an idiosyncratic response or that the subject had a pre-exposure/sensitization to the test material or component(s) of the test material or a cross-reactivity with a similar product/component. Data for such reactions will be included in the study report but will not be included in the final study analysis/conclusion of sensitization.

10.0 RESULTS AND DISCUSSION

(See Table 2 for Individual Scores)

A total of 55 subjects (11 males and 44 females ranging in age from 18 to 76 years) were empanelled for the testing procedure. Forty-nine (49/55) subjects satisfactorily completed the test procedure on Test Article: [redacted]. Six (6/55) subjects discontinued for personal reasons unrelated to the conduct of the study. Discontinued subject data are shown up to the point of discontinuation, but are not used in the Conclusions section of this final report.

Induction Phase Summary

Test Article	Induction Scores (Number of Responses)						Evidence of Irritation
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

Challenge Phase Summary

Test Article	Challenge Scores (Number of Responses)						Evidence of Sensitization
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

There was no skin reactivity observed at any time during the course of the study.

11.0 CONCLUSIONS

Under the conditions of a repeated insult (occlusive) patch test procedure conducted in 49 subjects, Test Article [redacted] was "Dermatologist-Tested" and was not associated with skin irritation or allergic contact dermatitis in human subjects.

[redacted]

[redacted]

TABLE 1

SUBJECT DEMOGRAPHICS

Test Article: [redacted]

Subject No.	Initials	Age	Sex	Race	Subject No.	Initials	Age	Sex	Race
1	TML	39	F	BA	29	CHL	60	M	BA
2	CAJ	64	F	BA	30	M-M	38	F	HS
3	R-H	47	F	BA	31	MBF	21	F	HS
4	CTS	72	F	CA	32	A-E	35	F	HS
5	JST	23	F	BA	33	M-R	35	F	HS
6	LSL	51	F	CA	34	M-W	54	F	BA
7	LNC	31	F	BA	35	MAC	53	M	CA
8	PBF	58	F	CA	36	L-M	72	F	CA
9	PJA	70	F	CA	37	BFB	21	M	CA
10	JLS	49	F	BA	38	JIC	71	F	CA
11	G-C	45	F	BA	39	E-G	70	F	CA
12	D-B	52	M	CA	40	MAM	58	F	CA
13	LJF	68	M	CA	41	E-P	74	F	BA
14	N-K	53	F	CA	42	A-J	50	F	CA
15	L-P	52	F	HS	43	M-D	29	F	CA
16	P-I	55	M	CA	44	LRK	44	F	CA
17	J-H	53	F	CA	45	A-R	34	F	CA
18	A-M	60	M	BH	46	JBD	18	F	BA
19	M-K	68	F	CA	47	S-C	44	F	BA
20	JAC	76	M	CA	48	DAP	21	M	BA
21	AEC	19	F	CA	49	FFM	24	F	BA
22	TAG	47	F	CA	50	B-P	54	F	BA
23	J-P	53	F	HS	51	LGH	57	F	BA
24	M-S	63	F	CA	52	BJG	58	F	CA
25	GCL	69	F	CA	53	M-M	63	F	CA
26	M-M	50	F	CA	54	A-H	66	F	BA
27	A-H	64	M	CA	55	JBD	18	M	BA
28	CCG	68	F	CA					

BA = Black/African American
BH = Black Hispanic
CA = Caucasian
HS = Hispanic

Shaded area = Discontinued subject

[redacted]

[redacted]

TABLE 2

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST – OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number 1	2	3	4	5	6	7	8	9	Challenge Virgin Site 24hr	72hr
1	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	Discontinued			
4	Discontinued										
5	Discontinued										
6	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	Discontinued									
11	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0

Scale:0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

[redacted]

TABLE 2 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST – OCCLUSIVE

Test Article: [redacted]

Subj.	Induction Evaluation Number									Challenge Virgin Site	
No.	1	2	3	4	5	6	7	8	9	24hr	72hr
31	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	Discontinued			
38	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0
41	Discontinued										
42	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0

Scale:0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: December 5, 2017

SUBJECT: Scientific Literature Review: Safety Assessment of Zinc Salts as Used in Cosmetics (posted October 12, 2017)

The following comments on the zinc salts Scientific Literature Review were received from a Council member company.

1) The CIR is incorrectly stating that BfR wanted Zn concentration in all oral care products to be lowered to 0.1% for adults. But in fact, BfR only asked for mouthwash to be lowered to 0.1% zinc. It may be simply misworded in the CIR draft, because they stated further up that BfR confirmed the safety of 1% Zn in toothpaste in adults.

2) CIR missed a 2013 study on 6-8 year old boys by Health Canada[1] (attached) that implies that the ULs for children are set too low (from the paper:"The absence of adverse effects in this study is noteworthy. When zinc intake from food and supplement is considered, all boys who received a zinc supplement had a total zinc intake exceeding the UL and many participants in the highest dose groups had intakes more than double the UL." and "These data provide evidence in support of the need for reexamining the current UL for zinc for children.").

3) The CIR kinetics section should be supplemented with the saturable absorption curve of zinc, i.e. the more zinc is ingested, the lower is the percentage of absorbed zinc (e.g. summarized by EFSA Scientific Opinion on Dietary Reference Values for zinc. 2014). This is unique to given essential elements vs xenobiotics, and very central to understanding systemic dose / dose responses in the context of zinc homeostasis.

---

[1]Bertinato J, Simpson JR, Sherrard L. 2013. Zinc supplementation does not alter sensitive biomarkers of copper status in healthy boys. *J Nutr* 143: 284-289.

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4) Table 5 (current frequency and concentration of use of zinc salts) should include oral care (toothpaste+mouthwash). Because the table is by salts, it might be sensible to create a sub-table to list oral care use not by salt but by zinc ion concentration.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: November 28, 2017

SUBJECT: Draft Report: Safety Assessment of Zinc Salts as Used in Cosmetics (draft prepared for the December 4-5, 2017 CIR Expert Panel Meeting)

Key Issue

Although recommended daily intakes are stated in the CIR report, and some information about the physiological role of Zinc is included in the report, it would be helpful if the report clearly stated that Zinc is essential. The inducible metal binding protein, metallothionein should also be mentioned somewhere in the report. For example, Zinc deficiency resulting from maternal metallothionein induction is a well known mechanism of developmental toxicity.[1]

Additional Considerations

Cosmetic Use - Please correct "Glumate"

Non-Cosmetic Use - It would be helpful to include the concentrations of these ingredients permitted in OTC skin protectant drug products (0.2-2% for Zinc Acetate; 0.2-2% for Zinc Carbonate).

[1]Hood RD. 2012. *Developmental and Reproductive Toxicology*, third edition. Informa Healthcare. London UK (see p. 594).

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Personal Care Products Council
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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Jay Ansell, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 22, 2018

SUBJECT: Tentative Report: Safety Assessment of Zinc Salts as Used in Cosmetics

The Council respectfully submits the following comments on the tentative report, Safety Assessment of Zinc Salts as Used in Cosmetics.

Acute, old report summary - As mg/l is a concentration the inhalation LD_{50} for Zinc Stearate should be an LC_{50}. As >200 mg/l (in the old report summary) is the same as >200,000 mg/m^3, it is likely that the study described with the new information is the same as that presented in the original report.

Short-Term, old report summary - What species was used in the 14-day dermal study? It says "guinea pigs" but then it says "a significant increase in body weight was reported in rats".

Developmental and Reproductive Toxicity - This section is misleading. Although too much zinc can cause adverse effects, it should also be made clear that zinc is essential for normal reproduction and development.

Clinical Studies - The study (reference 109) presented under the subheading "Retrospective and Multicenter Studies" is not a retrospective study. It is a "follow-up" or prospective study. The subjects were given supplemental zinc and followed for 14 years to determine outcome. The subheading "Retrospective and Multicenter Studies" is not necessary. What is the difference between "Clinical Studies" and "Clinical Reports"? It is not clear why the subheading "Clinical Reports" is needed under the "Clinical Studies" section heading.

Summary - Please revise: "...however not effects on weaning index, sex ratio, or litter size observed."

Please include the dose and route of exposure used in the study on Chester Beatty mice.

Discussion - The meaning of the following sentence is not clear. "The zinc ion drives the chemistry of these ingredients, and the lack of chemical reactivity accounts for biocompatibility." This sentence should be deleted. Zinc is essential. Biological

systems, including humans, control the "reactivity" of zinc by binding it to specific proteins. When there is too much zinc in the body, the body absorbs less and excretes more and produces a stress protein, metallothionien that sequesters excess zinc. Additional exposure to zinc from the use of zinc salts in cosmetics is not expected to exceed the range of levels that are considered to be essential.

Table 2 - As Citric Acid has been reviewed by CIR, it should be added to Table 2.

Table 3 - Based on the formula provided in Table 1 ($Zn_5(OH)_8Cl_2\ H_2O$), the formula weight given in Table 3 for Zinc Chloride Hydroxide (117.837) is not correct. The formula weigh for Zinc Cysteinate, 185.5446 also appears to be incorrect as the internet Chemical Book http://www.chemicalbook.com/ChemicalProductProperty_EN_CB7282535.htm gives a value of 305.69.

Table 5, footnote ** - As the information will not be "current" by the time the report was published, it would be better to use the date (2016/2017) the information was collected.

Table 8 - Two column headings are missing. For the *in vitro* study in pig skin, at what time point are the results reported?

Table 10, Inhalation - The rat study of Zinc Chloride (reference 14) states exposure concentrations in terms of zinc, but the LC_{50} is given in terms of Zinc Chloride. To be consistent with the dosing concentrations, it would be helpful to also state the LC_{50} in terms of zinc (952 mg Zn/m^3). Reference 14 says that 2 rats/group died after exposure to 940 and 1220 mg Zn/m^3, not one rat/group a stated in Table 10.

There is no information in the Zinc Laurate row. This row should be deleted or a study should be described in this row.

Table 11, Zinc Sulfate heptahydrate - If the NOEL in rats is 3000 ppm, it should state: "animals in groups fed ≤3000 ppm displayed no signs of treatment related effects" (< symbol needs to be changed to ≤).

Table 12, Zinc Chloride, reference 84 - The procedure column indicates that both males and females were treated. The results has information about pups born to "treated females", suggesting that there were groups in which only the females were treated. If both males and female rats were treated, "treated females" should be changed to "treated rats". If there were litters from just treated females mated to untreated males, the procedures need to be described in more detail.

Table 13, *in vitro* - It would be helpful if studies on one substances completed in the same cell type were presented together. For example, there are two studies of Zinc Chloride in *S. typhimurium*, the first one is the fourth Zinc Chloride study presented, the second is presented as the last (9^{th}) Zinc Chloride study presented.

Table 15 - Please define N/A at the end of the table.

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: January 29, 2018

SUBJECT: Tentative Report: Safety Assessment of Zinc Salts as Used in Cosmetic

The CIR Science and Support Committee (CIR SSC) appreciates the opportunity to comment on the tentative report on zinc salts.

After reviewing the CIR report on zinc salts, we are concerned that it is not clear that exposure to zinc from oral care products was considered. To make it clear that use of zinc salts in oral care products is included in the CIR report, please add a paragraph to the Cosmetic Use section about which zinc compounds and the zinc concentrations that are reported to be used in oral care products (non-drug toothpastes/dentifrices and non-drug mouthwashes). Exposure to zinc from oral care products should also be mentioned in the Discussion of the report.

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: February 1, 2018

SUBJECT: Tentative Report: Safety Assessment of Zinc Salts as Used in Cosmetic

We appreciate the opportunity to submit additional comments regarding the tentative CIR Safety Assessment of Zinc Salts as Used in Cosmetics. CIR's conclusion that current use practices are safe is well-drawn, and we believe that the data supporting this conclusion is strong. Addressing the below comments will improve the quality of the report.

In addition to mentioning use of zinc salts in oral care products in the Cosmetic Use section, zinc salts in oral care products should be specifically listed among other applications in the use survey data table. The terms "*incidental ingestion*" or "*mucous membrane*" used in Table 5 are too ambiguous and do not adequately identify the oral care use category. Besides intraoral application and a retained fraction after use, a limited, incidental dermal exposure is also possible in the perioral area. Other product types are identified by function (e.g. deodorant, hair-coloring) or product form (e.g. spray, powder). Thus, uses in dentifrice and oral rinse should be listed as such.

Under Clinical Studies, the CIR tentative report states: "*that the potential for long-term zinc supplementation to contribute to prostate carcinogenesis should be further investigated*". A meta-analysis of 17 studies (including 3 cohorts, 2 nested case-control, 11 case-control studies, and 1 randomized clinical trial, with a total of 111,199 participants and 11,689 cases of prostate cancer) indicated that there is no evidence for an association between zinc intake and prostate cancer (Mahmoud et al., 2016). The Health Professionals Follow-Up Study by Leitzmann et al., 2003 that is described in the tentative CIR report was included in this 2016 meta-analysis. Additionally, several detailed rebuttals to the Leitzmann et al., 2003 article, and others that link zinc with prostate cancer have been published (Krone and Harms, 2003; Chang et al., 2004; Costello et al., 2004; Costello and Franklin, 2007). The levels of zinc exposure from cosmetics product use is well below the level observed by Leitzmann et al., 2003 to have no association with prostate cancer. Therefore, we suggest that CIR revises its statement that further

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investigation is needed. The inclusion of the aforementioned studies will confirm the safety of zinc with regard to this endpoint.

We recognize that there is conflicting data for genotoxicity of zinc chloride. However, the biological activity is determined by the zinc cation. Genotoxicity data from other zinc salts is relevant in the overall risk assessment of zinc, and based on the available data, there is insufficient information to consider zinc as genotoxic. This conclusion might be a suitable addition to the CIR safety assessment. The CIR states "*Zinc Chloride was genotoxic in several in vivo assays using mice; statistically significant, dose-dependent increases were observed in chromosomal aberrations of bone-marrow cells (≤ 15 mg/kg), in sperm-head abnormalities (15 mg/kg), and in a Comet assay (eukaryotic cells; ≤ 9.95 mg/kg)*". The CIR reports conflicting results of genotoxicity of zinc, even in the same test systems. Many of these studies are mentioned in the EU 2004 risk assessment reports for zinc chloride and zinc sulphate (EU, 2004a; EU, 2004b). Although chromosomal aberrations were found *in vivo* in mouse studies with zinc chloride, two reliable micronucleus tests reported negative results in mice with zinc sulphate and in rats with zinc monoglycerolate (EU, 2004a; EU, 2004b). The negative micronucleus test in mice with zinc sulphate were at even higher intraperitoneal dose levels than seen in the mouse study which showed positive chromosomal aberrations following intraperitoneal dosing with zinc chloride (EU, 2004a ENREF 4; EU, 2004b). According to the EU 2004 Risk assessment report on zinc chloride, "*the positive sperm head abnormality test is considered sufficiently counter-balanced by two negative drosophila SLRL tests as well as two negative dominant lethal tests. Moreover, this sperm test is not adequately reported and without details on scoring criteria, interpretation of the observations is rather subjective. In addition, sperm head abnormalities are indicative rather than proof for genotoxicity*". This same report also stated that "*the positive result for chromosomal aberrations in vitro is considered over ruled by the negative in vivo tests for this endpoint....based on the available data there is insufficient ground to classify zinc as genotoxic....there is no clear evidence from the available data that zinc is genotoxic in vivo and without a clear indication for carcinogenicity.*" We consider these conclusions to be relevant for the safety assessment of zinc salts and respectfully request their consideration.

Finally, there has been a request that the CIR Expert Panel consider the addition of Zinc Oxide to the CIR report on zinc salts. In addition to its use as a colorant, sunscreen and skin protectant, Zinc Oxide may be used in cosmetics as a bulking agent, cosmetic biocide and oral care agent. The request noted that "with its solubility properties, Zinc Oxide is not too dissimilar from Zinc Phosphate and Zinc Stearate, both of which are included in the safety assessment. Most importantly, omitting Zinc Oxide from a review on zinc salts in cosmetics would be overlooking an important contributor to overall consumer zinc exposure from cosmetics. Its addition to the CIR report would create a more comprehensive review of zinc safety in cosmetics. Therefore, it is proposed that CIR consider including Zinc Oxide in the safety assessment of zinc salts as used in cosmetics."

References

Chang ET, Hedelin M, Adami HO, Gronberg H and Balter KA (2004) Re: Zinc supplement use and risk of prostate cancer. Journal of the National Cancer Institute 96:1108; author reply 1108-1109.

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