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Final Report on the Safety Assessment of Zinc Phenolsulfonate

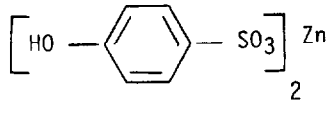
Zinc Phenolsulfonate is a substituted phenol used in cosmetic products as an antimicrobial and astringent at concentrations up to 5%. This compound was moderately toxic when administered orally. No deaths or growth inhibition were reported in a 91-day rat feeding study. No significant toxicity was reported when Zinc Phenolsulfonate was applied dermally in acute and subchronic studies. A single insult patch test of a 5% aqueous Zinc Phenolsulfonate solution was negative for skin irritation in rabbits. Minimal skin irritation was reported when 100% Zinc Phenolsulfonate was tested. The Buehler test for delayed sensitization was negative. No eye irritation was observed in rabbits exposed to 5% aqueous Zinc Phenolsulfonate and only moderate irritation at 100%.

No mutagenicity was observed when Zinc Phenolsulfonate was tested with and without metabolic activation in five *Salmonella* strains.

Clinical assessment of Zinc Phenolsulfonate with product formulations indicated that Zinc Phenolsulfonate was at most a mild skin irritant in normal use, but not a sensitizer. It is concluded that Zinc Phenolsulfonate is safe as a cosmetic ingredient in the present practices of use and concentration.

CHEMISTRY

Zinc Phenolsulfonate (CAS 127-82-2) is the substituted phenol that conforms to the following formula[1]:



Zinc Phenolsulfonate, also known as zinc sulfocarbolate, zinc sulphophenate, and zinc *p*-hydroxysulfonate, is normally available as the octahydrate in the form of white granules. It is odorless and is soluble in water, alcohol, and glycerol.[2,3] The compound has high UV absorptivity in the 200–300 nm range.[4] Chemical and physical data for Zinc Phenolsulfonate are presented in Table 1.

TABLE 1. Chemical and Physical Data for Zinc Phenosulfonate[2-4]

Molecular weight ($C_{12}H_{10}O_8S_2Zn$)	411.7
(as octahydrate $C_{12}H_{10}O_8S_2Zn(H_2O)_8$)	555.8
Assay (as $C_{12}H_{10}O_8S_2Zn$)	73.7–77.4%
Zinc	11.8 ± 0.1%
Sulfate	0.4% (max)
Iron	0.0005% (max)
pH (1 g in 250 ml water)	5.5 (min)
Arsenic	0.0008% (max)
Lead	0.001% (max)
Calcium	<100 ppm
Magnesium	<100 ppm
Manganese	<100 ppm
Nickel	<100 ppm
Silicon	<100 ppm
Barium	<10 ppm
Copper	<10 ppm
Iron	<10 ppm
Cadmium	<1 ppm
Appearance	White granules
Odor	Odorless

Zinc Phenolsulfonate is "compatible" with small amounts of alkalies or acids. It is incompatible with alkali soaps, since large amounts of alkali will cause precipitation of zinc hydroxide or formation of zincates. In the presence of ammonia, diamine zinc complexes may form.[2] Zinc Phenolsulfonate, as the octahydrate, effluoresces in dry air and loses all of its H_2O at about 120°C.[3]

Zinc Phenolsulfonate is prepared by a proprietary process.[2] Some grades of Zinc Phenolsulfonate may contain up to 5% of free phenolsulfonic acid.[5] Heavy metal concentrations are below toxicological significance[4] (Table 1).

USE

Noncosmetic Use

Zinc Phenolsulfonate was formerly used as an intestinal antiseptic in doses of 60–200 mg.[6] It was used externally to promote healing of ulcers and slowly granulating wounds.[3] Zinc Phenolsulfonate is currently used in insecticide formulations.[6]

Zinc Phenolsulfonate has been reviewed by the Over-the-Counter (OTC) drug review conducted by the FDA. The Laxative Panel concluded Zinc Phenolsulfonate was Category IIIE (insufficient data) for antidiarrheal use and Category IIE (not generally recognized as effective or is misbranded) for antiemetic use. The Miscellaneous External Panel determined Zinc Phenolsulfonate was Cate-

gory IISE (not generally recognized as safe and effective or is misbranded) for external analgesic and skin protectant use.[7]

The Cosmetic Ingredient Review determines the safety of ingredients used in cosmetic products. The OTC Drug Review conducted by the FDA determines both the safety and effectiveness of specific ingredients for specific drug claims. Part of FDA's judgment regarding drug ingredient safety is the use of benefit-to-risk considerations. This is not the case for cosmetic ingredient safety as determined by CIR. Safety judgments are based solely on an assessment of the available safety data. Thus, the same substance may be considered by both CIR and FDA. The uses are different, as is the basis upon which safety judgments are made. As a result, the two scientific panels may well reach different conclusions about the same substance.

Cosmetic Use

Zinc Phenolsulfonate is used in cosmetics as an antimicrobial and as an astringent.[5,8] The ingredient is used in such products as personal deodorants, aftershave lotions, skin fresheners and tonics, body and foot powders, and astringent creams and lotions.[9] Data submitted to the Food and Drug Administration in or before 1981 by cosmetic firms participating in the voluntary cosmetic registration program indicated that Zinc Phenolsulfonate was used in a total of 67 of the registered products at reported concentrations ranging from $\leq$0.1% to >1–5%. The largest number of reported uses was in underarm deodorant formulations (40)[9] (Table 2).

The cosmetic product formulation listing that is made available by the FDA is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[10] Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Since data are only submitted within the framework of preset concentration ranges, the opportunity exists for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

Cosmetics containing this ingredient are applied to all areas of the skin. These cosmetics are frequently applied to the face and have the potential for coming into contact with the eye or being ingested. Products containing this ingredient are applied daily and can remain in contact with the skin for long periods of time.

TABLE 2. Product Formulation Data for Zinc Phenosulfonate[9]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)			
			Unreported concentration	>1-5	>0.1-1	≤0.1
Fragrance powders (dusting and talcum, excluding aftershave talc)	483	5	–	2	3	–
Deodorants (underarm)	239	40	–	36	4	–
Aftershave lotions	282	4	–	2	2	–
Shaving cream (aerosol, brushless, and lather)	114	3	3	–	–	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	2	–	1	1	–
Moisturizing skin care preparations	747	1	–	–	–	1
Paste masks (mud packs)	171	1	–	1	–	–
Skin fresheners	260	9	–	2	3	4
Other skin care preparations	349	2	–	2	–	–
1981 TOTALS		67	3	46	13	5

TOXICOLOGY

Oral Studies

Acute Oral Toxicity

A 33.3% aqueous solution of Zinc Phenolsulfonate was administered by stomach tube to female albino rats. The observation period was 7 days. In one test, a single 1.0 g/kg dose killed 1/5 rats within 48 h[11]; in another test, a single 2.15 g/kg dose killed 4/5 rats within 24 h.[12] The 5.0 g/kg dose killed 5/5 rats within 24 h.[13] An oral LD_{50} for rats of 1.8 g/kg was estimated from these studies (Table 3).

The acute toxicity of a 20% (w/w) aqueous solution of Zinc Phenolsulfonate was evaluated in Cox CD rats. Five doses ranging from 0.95 to 3.64 g/kg were administered orally to groups of 10 rats each. The observation period was 14 days. Doses of 0.95, 1.33, 1.86, 2.60, and 3.64 g/kg killed 0/10, 2/10, 5/10, 9/10, and 9/10, respectively. The oral LD_{50} for rats was 1.8 g/kg[14] (Table 3).

Zinc Phenolsulfonate dissolved in 0.25% agar to a final concentration of 0.5 g/ml was administered orally to male CF-1 albino mice. Single doses of 10 g/kg and 5.472 g/kg killed 10/10 mice each. Five of 10 mice receiving 3.0 g/kg died,

TABLE 3. Oral Studies with Zinc Phenosulfonate

Test	*Zinc Phenolsulfonate concentration*	*Dose*	*Animal*	*Comments*	*Reference*
Acute LD_{50}	33.3% aqueous solution	1.0, 2.15, 5.0 g/kg	Rats (5 per dose)	1.8 g/kg oral LD_{50}	11–13
Acute LD_{50}	20% aqueous solution	0.95, 1.33, 1.86, 2.60, 3.64 g/kg	Rats (10 per dose)	1.8 g/kg oral LD_{50}	14
Acute LD_{50}	500 mg/ml of 0.25% agar solution	1.645, 3.0, 5.472, 10.0 g/kg	Mice (10 per dose)	3 g/kg oral LD_{50}	15
Acute LD_{50}	3.5% in a deodorant	5, 10, 15 g/kg	Rats (5 per dose)	12.1 g/kg oral product LD_{50}	16–18
91-day subchronic	Undiluted	62.5, 250, 1000 mg/kg per day	Rats (40 weanlings per dose)	See text re possible testicular abnormalities; no other adverse effects	19

whereas none receiving 1.534 g/kg died. An oral LD_{50} for mice of 3.0 g/kg was estimated[15] (Table 3).

A concentrate of an aerosol deodorant containing 3.5% Zinc Phenolsulfonate (propellant evaporated) was evaluated for acute toxicity in female rats. Single doses of 5.0, 10.0, and 15.0 g deodorant/kg were administered by oral intubation to groups of five rats each, followed by a 7-day observation period. No deaths resulted from administration of 5.0 and 10.0 k/kg. All five of the rats died after the 15 g/kg dose was administered. An oral LD_{50} of 12.1 g/kg was calculated for the deodorant[16–18] (Table 3).

Subchronic Oral Toxicity

Diets containing Zinc Phenolsulfonate were fed to weanling COX-SP albino rats of both sexes. Test groups consisting of 40 weanling rats each were fed 62.5, 250, and 1,000 mg/kg per day of Zinc Phenolsulfonate for 91 days. Controls (180 rats) were fed the basal laboratory diet. No unusual variation in feed consumption, growth, or hematological values were reported. Organ:body weight ratios were normal, and observed variations were randomly distributed. Histological abnormalities of testicular tissues were reported for all three treatment groups at the 4 week necropsy interval. Of the three males fed low dosages and necropsied, two were reported to have increased interstitial fluid in the testes. The three intermediate-dose males all had increased testicular interstitial fluid, and two had hydropic changes in the seminiferous tubules. The three high-dose males all had increased testicular interstitial fluid, and one was reported to have vacuolar changes in the seminiferous tubules. No testicular abnormalities were observed in males necropsied at the 8-week interval and at the end of the study. No other significant treatment-related effects were reported.[19]

Percutaneous Studies

Acute Dermal Toxicity

Zinc Phenolsulfonate at a concentration of 25% in aqueous solution was applied to the clipped skin of six albino guinea pigs. On three of the animals, epidermal abrasions were made at the exposure site. The animals were treated with a 3.0 g/kg dose for 24 h, and the test sites were covered by occlusive patches. During the 7-day observation period, no animals died, and the material was classified as nontoxic by percutaneous application[20] (Table 4).

Subchronic Dermal Toxicity

In a 28-day percutaneous study, a 12.5% aqueous solution of Zinc Phenolsulfonate was applied to the abraded skin of restrained New Zealand rabbits. A 2.0 ml/kg per day dose of a 12.5% (w/v) Zinc Phenolsulfonate solution and of an undiluted solution of propylene glycol were applied separately to groups of six rabbits each. Mild to moderate erythema was observed at all test sites in both groups. No test-related abnormalities were observed at necropsy in the Zinc Phenolsulfonate test group.[21]

A 91-day percutaneous study in rabbits was conducted to determine the toxicity of an aerosol deodorant containing 2% (w/w) Zinc Phenolsulfonate. Two g/kg per day was sprayed on the shaved backs of five male and five female New Zealand white rabbits. The compound was applied 5 days/week for 13 weeks, for a total of 65 applications. A control group of five male and five female rabbits was exposed to distilled water. Slight erythema was noted for all of the treated rabbits after Day 8 of the study period and persisted for 1–10 days. Slight edema was described for all but one of the rabbits. Slight atonia was reported in three rabbits, slight desquamation was observed in eight rabbits, "slight coriaceousness" was reported in five rabbits, and slight fissuring was noted in six rabbits. The skin of the treated rabbits was comparable to the skin of the control rabbits

TABLE 4. Dermal Toxicity of Zinc Phenolsulfonate

Test	*Zinc Phenolsulfonate concentration*	*Test material dose*	*Number of animals*	*Comments*	*Reference*
Acute	25% aqueous solution	3.0 g/kg	6 guinea pigs	No deaths	20
28-day subchronic	12.5% aqueous solution	2.0 ml/kg per day	6 rabbits	No test-related effects	21
91-day subchronic	2% in a deodorant	2 g/kg per day	10 rabbits	Slight edema and erythema; no other test-related effects	22
91-day subchronic	1% in an astringent	3.4 g/kg per day	20 rats	Slight drying and erythema; no other treatment-related effects	23

when examined microscopically. No treatment-related changes were reported for body weights, organ weights, tissues, or hematological values.[22]

An astringent containing 1% Zinc Phenolsulfonate was applied to albino rats in a 13-week dermal toxicity study. Ten male and ten female rats were dosed with 3400 mg/kg per day of the astringent on the clipped scapular region 5 days/week for 13 weeks. No attempt was made to preclude ingestion. An equal number of control animals were treated with distilled water using the same treatment schedule. Slight erythema and drying of the skin were observed throughout the study in the test rats. Body weights of the treated animals were comparable to those of controls, and no treatment-related effects were observed at necropsy or after histopathological examinations of selected tissues. Results of urinalysis were negative for treatment-related alterations. Serum glucose, hematocrit, hemoglobin concentration, and red blood cell count did differ significantly from control values, but the differences were reportedly not test related[23] (Table 4).

Intraperitoneal Studies

Acute Intraperitoneal Toxicity

Zinc Phenolsulfonate dissolved in 0.25% agar was given by intraperitoneal injection to groups of 10 male albino CF-1 mice. At doses of 100 and 132 mg/kg, none of the mice died. Doses of 173 and 300 mg/kg killed 8/10 and 9/10 mice, respectively. The intraperitoneal LD_{50} for mice was 172 mg/kg (95% C.L. = 140.98–209.84 mg/kg).[15]

Acute intraperitoneal toxicity testing of a 10% (w/w) aqueous solution of Zinc Phenolsulfonate was conducted with Cox CD rats. At a dose of 150 mg/kg, 3/10 rats died; doses of 225 and 338 mg/kg each killed 6/10 rats; and a 500 mg/kg dose killed 9/10 rats. The intraperitoneal LD_{50} for rats was 225 mg/kg.[24]

Inhalation Studies

Acute Inhalation Toxicity

An underarm aerosol deodorant (3.5% Zinc Phenolsulfonate) was tested for acute inhalation toxicity in two separate studies.[25,26] Treatment and control groups each consisted of six female Sprague-Dawley albino rats. The animals were exposed for a total of 1 h (four 15-minute intervals) in a static inhalation chamber. In one experiment, exposure to a static atmospheric concentration of 205 mg/L resulted in no deaths during the 7-day observation period.[26] No deaths were reported in the second experiment after exposure to 208 mg/L in a static system.[25] Particle size was not stated in either case. The deodorant was classified as nontoxic by inhalation (Table 5).

A foot spray containing 1.65% Zinc Phenolsulfonate was tested using the same method.[26] No deaths were observed after exposure of six rats to a 203 mg/L product concentration for 1 h. The spray was classified as nontoxic by inhalation[27] (Table 5).

Twenty adult albino rats (10M, 10F) were exposed by inhalation to an aerosol deodorant containing 1.98% Zinc Phenolsulfonate. The animals were dosed

TABLE 5. Inhalation Toxicity of Products Containing Zinc Phenolsulfonate

Test	*Zinc Phenolsulfonate concentration*	*Exposure concentration*	*No. of animals*	*Comments*	*Reference*
Acute, static chamber	3.5% in a deodorant	205 mg/L for 1 h	6 Rats	No deaths	26
Acute, static chamber	3.5% in a deodorant	208 mg/L for 1 h	6 Rats	No deaths	25
Acute, static chamber	1.65% in a foot spray	203 mg/L for 1 h	6 Rats	No deaths	27
Acute, dynamic chamber	1.98% in a deodorant	166.4 mg/L for 1 h	20 Rats	No deaths, all animals completely recovered by Day 9	28
Acute, plethysmograph	1.98% in a deodorant	2 1-minute sprays	8 Mice	Decreased respiratory rate, recovered within 30 minutes	29
Subchronic 13-week	1.65% in a foot spray	20 mg/m^3 4 h/day, 5 days/week	24 Rats	Decreased organ:body weight ratio for brain and liver in females, testes in males	30
Subchronic 13-week dynamic chamber	2.84% in a deodorant	10, 45 mg/m^3 3 h/day, 7 days/week	20 Guinea pigs	Dry and moist rales, kidney:body weight ratio depressed in high-dose females	31
Subchronic 13-week dynamic chamber	2.84% in a deodorant	6, 36 mg/m^3 3 h/day, 7 days/week	12 Monkeys	Coughing, macrophage accumulation	32

with a calculated concentration of 166.4 mg/L for 1 h in a dynamic chamber. An equal number of control rats were exposed to room air in a second chamber. All animals survived the 14-day observation period. Depression, ptosis, ataxia, labored respiration, and subconvulsive jerking were observed in all test animals immediately after exposure. All animals had recovered completely by Day 9. Pulmonary lesions were observed at necropsy in both test and control animals and were considered the result of intercurrent disease processes. At microscopic examination of tissues, no compound-related effects were observed[28] (Table 5).

The upper respiratory tract irritancy of two aerosol deodorants containing 1.98% Zinc Phenolsulfonate was evaluated in albino mice. Test groups of four mice each were placed in plethysmographs with their heads projecting into a central exposure chamber. The mice were exposed to two 1-minute sprays of the deodorant administered 5 minutes apart, followed by a 30-minute observation period. The 1-minute exposures to the first deodorant resulted in a 60–80% decrease in respiratory rate. Respiration returned to normal by the end of the ob-

servation period. Exposure to the second deodorant formulation resulted in 50–70% decreases in respiratory rates. The breathing rates returned to normal during the observation period[29] (Table 5).

Subchronic Inhalation Toxicity

In a 13-week study, albino rats of each sex were used to study the effects of inhalation of a foot spray containing 1.65% Zinc Phenolsulfonate. The treatment and control groups each contained 24 rats. A 20 mg/m^3 (20 μg/L) exposure was administered 4 hours/day, 5 days/week for 65 treatment days. The average particle size was 3.4 microns, and, therefore, inhalation into the deep lung (alveoli) would be expected. All rats survived the study. Body weights and hematological values were significantly elevated in test animals but were within the range of historical controls for this strain in the laboratory. No adverse effects on behavior, clinical chemistry, or urinalysis values were reported. No gross changes were observed at necropsy. Significant decreases were observed in organ:body weight ratios of the brain and liver in treated females and of the testes in treated males. No compound-induced changes were observed at microscopic examination of tissues[30] (Table 5).

A 13-week inhalation toxicity study of an aerosol deodorant containing 2.84% Zinc Phenolsulfonate was performed in a dynamic inhalation chamber. Two treatment groups of 20 Hartley guinea pigs were exposed to the product 3 hours/day, 7 days/week for 13 weeks. The measured chamber atmosphere concentrations were 10 mg/m^3 (10 μg/L) for the low-dose group and 45 mg/m^3 (45 μg/L) for the high-dose animals. An average mass median diameter of 2.9–3.3 microns was determined for the generated aerosols. A sham air-exposed control group consisted of 40 guinea pigs. No significant treatment-related deaths, body weight changes, or feed consumption changes were reported. Both dry and moist rales were observed in the exposed animals. The kidney:body weight ratio of the high-dose female guinea pigs was significantly depressed. No significant treatment-related lesion was observed at necropsy or after microscopic examination of the tissues. Morphological changes of chronic respiratory disease were reported in both control and treated animals.[31]

An aerosol deodorant containing 2.84% Zinc Phenolsulfonate was administered by inhalation to cyanomologus monkeys (*Maccaca fasicularis*) for 90 days. Two test groups of four males and five females were exposed to 6 and 36 mg/m^3 (6 and 36 μg/L) for 60 minutes three times per day at 2-hour intervals, 7 days/week for 13 weeks. Particle size analysis with a Battelle Cascade Impactor indicated that less than 50% of the aerosol particles were within the respirable range (<5 microns). No deaths occurred during the study. All of the high-dose monkeys were observed coughing. No exposure-related effects were observed during pulmonary function tests. No significant changes in hematological, serum chemistry, or urinalysis values were reported. Body and organ weights were comparable between test and control animals. Exposure-related pulmonary changes observed at histopathological examination consisted of a dose-dependent accumulation of macrophages within the bronchiolar and alveolar walls and focal accumulation of free alveolar macrophages[32] (Table 5).

Skin Irritation

The skin irritancy of a 5% aqueous Zinc Phenolsulfonate solution was evaluated in female albino rabbits by a single insult patch test. A filter disc containing 0.5 ml of the test solution was applied under an occlusive dressing to the clipped back of each of nine rabbits. The dressing was removed after 24 h. The test sites were graded for irritation and edema 26 and 48 h after application. The group Primary Irritation Index (PII) was 0/4.0, indicating no skin irritation[33] (Table 6).

"One hundred percent" Zinc Phenolsulfonate (dose not specified) was evaluated using a similar procedure. A group PII of 1.17/4.0 was reported, indicating minimal skin irritation[34] (Table 6).

A deodorant containing 3.5% Zinc Phenolsulfonate was evaluated by means of a single insult occlusive patch test. No skin irritation was observed (PII = 0)[35] (Table 6).

A deodorant formulated with 1.94% Zinc Phenolsulfonate was tested for skin irritation using six rabbits by means of the Draize procedure.[36] For each rabbit two clipped test sites, one intact and one abraded, were treated with 0.5 ml of product and covered by an occlusive patch. The material was removed after 24 h. The sites were scored 24 and 72 h after application. A PII of 0/8 was reported, indicating no irritation[37] (Table 6).

A deodorant containing 1.98% Zinc Phenolsulfonate was evaluated for irritation in six rabbits by standard Draize procedures.[36] A PII of 1.66/8.0 was reported, indicating mild irritation[38] (Table 6).

Skin Sensitization

The delayed sensitivity potential of Zinc Phenolsulfonate was evaluated using the procedures described by Buehler.[39] The test group consisted of 20 Hartley albino guinea pigs and the control of 10 Hartley albino guinea pigs.

TABLE 6. Skin Irritation of Zinc Phenolsulfonate

Test	*Zinc Phenolsulfonate concentration*	*No. of animals*	*PII*[a]	*Comments*	*Reference*
Single insult occlusive patch	5% aqueous solution	9 female rabbits	0/4	No irritation	33
Single insult occlusive patch	100%	9 female rabbits	1.17/4	Minimal irritation	34
Buehler delayed sensitivity	16% in ethanol or acetone	20 Hartley guinea pigs	– – –	No irritation or sensitization	40
Single insult occlusive patch	3.5% in a deodorant	9 female rabbits	0/4	No irritation	35
Draize irritation	1.94% in a deodorant	6 rabbits	0/8	No irritation	37
Draize irritation	1.98% in a deodorant	6 rabbits	1.66/8	Mild irritation	38

[a]PII, Primary Irritation Index.

A 0.5 ml dose of a 16% (w/v) Zinc Phenolsulfonate and ethanol solution was applied to the clipped back skin of the test animals. Three exposures of 6 h each comprised the induction phase. After a 2-week nontreatment period, a challenge patch was applied to the site using a 16% (w/v) solution of the test material in acetone. The test sites were scored 24 and 48 h after application of the challenge patch. No skin irritation or sensitization reactions were reported[40] (Table 6).

Eye Irritation

A 5% aqueous Zinc Phenolsulfonate solution was instilled into the eyes of six albino rabbits. A 0.1 ml dose was applied without a subsequent water rinse. No eye irritaiton, as evaluated by the Draize scoring system,[36] was observed[41] (Table 7).

"One hundred percent" Zinc Phenolsulfonate (dose not specified) was instilled into the eyes of each of six rabbits. The treated eyes received no water rinse. Scores of 36, 32, 39, 54, and 50 (max = 110) were reported for the respective 1, 2, 3, 4, and 7-day periods following administration. The eye irritation potential was considered moderate[42] (Table 7).

Two groups of three New Zealand albino rabbits were administered 3 mg of "undiluted" Zinc Phenolsulfonate. The first group was administered the compound into the eye without a subsequent water rinse. A maximum average score of 22.3 was reported, indicating moderate irritation. Two rabbits recovered in 3 days, and one rabbit recovered after 4 days. The second group was administered the compound, and the eyes were rinsed with water afterward. A maximum average score of 6.0 was reported, indicating mild irritation. All rabbits recovered after 1 day.[43] The maximum possible score for this study was not reported (Table 7).

TABLE 7. Ocular Irritation of Zinc Phenolsulfonate

Zinc Phenolsulfonate concentration	*Test material dose*	*Water rinse*	*No. of rabbits*	*Average irritancy score*	*Day of ocular clearing*	*Reference*
5% in aqueous solution	0.1 ml	No	6	0	1	41
100%	Not specified	No	6	54	>7	42
"Undiluted"	3 mg	No	3	22.3	4	43
"Undiluted"	3 mg	Yes	3	6.0	1	43
1.98% in a deodorant	1-second spray	No	5	21	7	43
2% in a deodorant	2-second spray	No	3	0	1	45
2% in a deodorant	2-second spray	Yes	3	0	1	45
1.94% in a deodorant	2 brief bursts of spray	No	3	Slight to moderate irritation	4	46

A deodorant containing 1.98% Zinc Phenolsulfonate was evaluated for eye irritation in five New Zealand white rabbits. The left eye of each animal was exposed to a 1-second spray of the product from a distance of 6 inches. The eyes were not rinsed with water after exposure. An average irritancy score of 21 was reported. Irritation had dissipated by the seventh day (Table 7). The deodorant was classified as a mild irritant by the Draize classification[36,44] (Table 7).

An aerosol formulation containing 2% Zinc Phenolsulfonate was sprayed into the eyes of six rabbits. The rabbits received a 2-second spray of the product from a distance of 6 inches. Three rabbits received a water rinse 4 seconds after application, and three rabbits received no water rinse. No irritation was observed[45] (Table 7).

A deodorant spray containing 1.94% Zinc Phenolsulfonate was sprayed into the eyes of three rabbits. Two separate, brief bursts of the spray from a distance of 6 inches constituted the dose. Slight to moderate irritation was observed during the initial 24 h, and no irritation or slight irritation was observed during the 24–96 h after exposure[46] (Table 7).

MUTAGENICITY

Zinc Phenolsulfonate was tested in the *Salmonella*/Microsomal Mutagenicity Plate Incorporation Assay with *Salmonella* strains TA1535, TA1537, TA1538, TA98, and TA100. Doses of 5000, 1000, 500, and 50 μg per plate were evaluated with and without S-9 metabolic activation. No mutagenicity was observed.[47]

CLINICAL ASSESSMENT OF SAFETY

An underarm deodorant containing 3.5% Zinc Phenolsulfonate was evaluated for irritation using a panel of 18 subjects by means of a single insult patch test. The test material was applied for 24 h to the arm under an occlusive patch. Skin reactions were evaluated 2 and 24 h after removal of the patches, and a group PII was calculated. No irritation was observed.[48]

Using the same procedure, a foot spray containing 3% Zinc Phenolsulfonate was evaluated for skin irritation using a panel of 18 subjects. Mild irritation was observed in 1 subject. An average score of 0.06/4.0 was reported.[49]

Two dandruff shampoo products containing 1% Zinc Phenolsulfonate were evaluated for skin irritation using a panel of 37 subjects. No irritation was observed to either product after application to the skin.[50,51]

An astringent containing 1% Zinc Phenolsulfonate was evaluated in a cumulative irritancy test.[52] Occlusive patches containing the test material were applied for 23 h to the backs of 13 panelists for 21 consecutive days. A total score of 56.92/630 was observed, indicating that the irritancy of the test material was "probably mild in normal use."[53]

A study of the cumulative irritant properties of an astringent containing 1.25% Zinc Phenolsulfonate was performed by the methods of Phillips et al.[52] using an 11-member panel. A score of 312.73/630 was reported, indicating that the irritancy of the product was "possibly mild in normal use."[54]

Repeat insult patch test procedures were used to evaluate two astingents containing 1% Zinc Phenolsulfonate. Nine occlusive patches were applied for 24 h to the same sites over a 3-week induction period. Following a 2-week nontreatment period, a challenge patch was applied for 24 h to a previously untreated site. Reactions were evaluated 24 and 48 h after removal of the patch. One astringent was negative for irritation and sensitization in all 100 subjects.[55] For the second astringent, barely perceptible to mild skin erythema was reported during the induction phase for 15/86 subjects. No sensitization was observed.[56]

An astringent containing 1.25% Zinc Phenolsulfonate was evaluated by means of the repeat insult patch test.[55] No skin irritation or sensitization was observed in 87 panelists.[57]

A foot spray concentrate containing 1.65% Zinc Phenolsulfonate was evaluated for sensitization in a repeat insult patch test.[55] Barely perceptible skin erythema was noted in 3 of 48 individuals. No skin sensitization was observed.[58]

A repeat insult patch test of two deodorants containing 2% Zinc Phenolsulfonate was performed using a 76-member panel by the procedures previously described.[55] Challenge reactions were observed in 2 subjects. One subject strongly reacted to both formulations, and the second subject reacted only to the second formulation.[59] At rechallenge, the subject with the strong reaction was hyperreactive to alcohol. The second subject did not react to rechallenge applications, indicating that this subject was not sensitized.[60]

A 116-member panel was used to evaluate a deodorant concentrate containing 4.18% Zinc Phenolsulfonate. Repeat insult patch test procedures described earlier[55] were employed. The results were negative for skin sensitization.[61]

The concentrate of a deodorant containing 2.75% Zinc Phenolsulfonate was evaluated by means of the repeat insult patch test procedures of Draize.[36] Semi-open rather than occlusive patches were used. No sensitization was reported in 53 subjects.[62]

Two deodorants containing 2.57% Zinc Phenolsulfonate were evaluated with repeat insult patch tests and a 53-member panel. Nine occlusive patches of each formulation were applied for 24 h over a 3-week period. Following a 10-day nontreatment period, a challenge patch was applied for 24 h to an untreated site. The sites were examined for reactions immediately after removal of the challenge patch, and at 24 and 48 h after patch removal. No skin irritation or sensitization was observed to either formulation.[63]

Two deodorants containing 2.75% Zinc Phenolsulfonate were each evaluated by repeat insult patch procedures using 50-member panels. Six 24-h patches in a 2-week induction period, a 2-week nontreatment period, and a 24-h challenge patch comprised the treatment regimen. No skin irritation or sensitization was reported for either formulation.[64,65]

A repeat insult patch test of an aerosol deodorant concentrate (3.98% Zinc Phenolsulfonate) was conducted using a 71-member panel. Nine 24-h induction patches were followed by a 2-week nontreatment period. A challenge patch was applied for 24 h, and the subjects were observed for sensitization. One subject reacted to the challenge patch. Results of a rechallenge patch test indicated that the subject was presensitized to alcohol.[66]

The sensitization potential of an aerosol deodorant (2.75% Zinc Phenolsulfo-

nate) was evaluated with repeat insult patch test procedures and a 54-member panel. Eight induction patches and a 2-week nontreatment period followed by a single challenge patch comprised the treatment schedule. No skin sensitization was observbed.[67]

The clinical studies are summarized in Table 8.

SUMMARY

Zinc Phenolsulfonate is a substituted phenol commonly used in cosmetic products for its antimicrobial and astringent properties. The largest number of reported uses was as an ingredient of underarm deodorants. Reported concentrations in cosmetics ranges from ≤0.1 to >1–5%.

This compound was moderately toxic when administered orally. The acute oral LD_{50} for rats was 1.78 g/kg, whereas the acute oral LD_{50} for mice was 3 g/kg. The intraperitoneal LD_{50} for mice was 172 mg/kg. In a 91-day feeding study, rats were fed 62.5, 250, and 1000 mg/kg per day. No deaths or growth inhibition were reported. Testicular alterations were observed in males necropsied after 4 weeks of feeding but were not observed in rats killed after 8 weeks or those killed at the end of the study. These changes were considered of no toxicological significance.

Significant toxicity was not reported when Zinc Phenolsulfonate was applied dermally. In an acute study, 3 g/kg applied to the skin of guinea pigs did not cause any deaths. In a 28-day subchronic study, 2 ml/kg per day of a 12% Zinc Phenolsulfonate solution was applied to the skin of rabbits. Mild erythema was reported, but no test-related lesions were observed at necropsy.

Inhalation studies were performed with cosmetic products containing Zinc Phenolsulfonate. In acute studies, rats were exposed to chamber concentrations of 166 to 208 mg/L of product aerosol sprays. No deaths were reported in four separate studies. In a subchronic study, rats were exposed to 20 mg/m^3 of a product aerosol spray for 13 weeks. Depressed brain, liver, and testes organ: body weight ratios were reported, but no compound-related tissue changes were observed. Guinea pigs were exposed to 10 and 45 mg/m^3 of an aerosol product for 13 weeks. Possible interim testicular effects were observed that were not confirmed at the end of the study. In a 90-day subchronic study, monkeys were exposed to an aerosol product at concentrations of 6 or 36 mg/m^3. A dose-dependent accumulation of macrophages in the lungs was reported.

A single insult patch test of a 5% aqueous Zinc Phenolsulfonate solution was negative for skin irritation in rabbits. Minimal skin irritation was reported when 100% Zinc Phenolsulfonate was tested using the same procedures. The Buehler test for delayed sensitization was negative when a 16% Zinc Phenolsulfonate in ethanol solution was applied to the skin of guinea pigs.

No eye irritation was observed in rabbits exposed to a 5% aqueous Zinc Phenolsulfonate solution. Moderate irritation was observed when 100% Zinc Phenolsulfonate was applied to rabbit eyes; however, the irritation persisted through the 7-day observation period.

Zinc Phenolsulfonate (100%) instilled into rabbit eyes without subsequent water rinse produced moderate ocular irritation. When the eyes were rinsed with water after application of the compound, mild eye irritation was observed.

TABLE 8. Skin Irritation and Sensitization to Products Formulated with Zinc Phenolsulfonate

Test	*Zinc Phenolsulfonate concentration*	*No. of panelists*	*Results*	*Reference*
Single insult occlusive patch	3.5% in a deodorant	18	No skin irritation	48
Single insult occlusive patch	3% in a foot spray	18	Average score, 0.06/4.0; mild skin irritation	49
Single insult occlusive patch	1% in a dandruff shampoo	37	No skin irritation	50
Single insult occlusive patch	1% in a dandruff shampoo	37	No skin irritation	51
Cumulative irritancy	1% in an astringent	13	Score, 56.92/630; probably mild skin irritation in normal use	53
Cumulative irritancy	1.25% in an astringent	11	Score, 312.73/630; possibly mild skin irritation in normal use	54
Repeat insult patch test	1% in an astringent	100	No skin irritation or sensitization	55
Repeat insult patch test	1% in an astringent	86	Barely perceptible to mild skin erythema in 15 panelists; no skin sensitization	56
Repeat insult patch test	1.25% in an astringent	87	No skin irritation or sensitization	57
Repeat insult patch test	1.65% in a foot spray concentrate	48	Barely perceptible skin erythema in 3 panelists; no skin sensitization	58
Repeat insult patch test	2% in a deodorant (2 formulations)	76	2 panelists reacted to challenge; a rechallenge test was conducted, and 1 panelist was sensitized to alcohol, and the other panelist did not react to the rechallenge	59,60
Repeat insult patch test	4.18% in a deodorant concentrate	116	No skin irritation or sensitization	61
Repeat insult patch test	2.75% in a deodorant concentrate	53	Using semi-open patches, no skin sensitization	62
Repeat insult patch test	2.57% in a deodorant	53	No skin irritation or sensitization	63
Repeat insult patch test	2.57% in a deodorant	53	No skin irritation or sensitization	63
Repeat insult patch test	2.75% in a deodorant	50	No skin irritation or sensitization	64
Repeat insult patch test	2.75% in a deodorant	50	No skin irritation or sensitization	65
Repeat insult patch test	3.98% in a deodorant	71	1 panelist reacted to challenge patch; a rechallenge test determined the panelist was sensitized to alcohol	66
Repeat insult patch test	2.75% in a deodorant	54	No skin sensitization	67

No mutagenicity was observed when Zinc Phenolsulfonate was tested with and without metabolic activation in five *Salmonella* strains.

Clinical assessment of Zinc Phenolsulfonate was conducted entirely with product formulations. Single insult occlusive patch tests were performed with a total of 110 subjects from four studies. Mild skin irritation was observed in 1 subject. The results of cumulative irritancy tests with 24 subjects from two studies indicated that Zinc Phenolsulfonate was "probably" or "possibly" a mild skin irritant in normal use. Repeat insult patch tests used 844 total subjects and 12 product formulations were evaluated. Reactions were observed at challenge in 3 subjects, of whom 2 were sensitized to alcohol.

CONCLUSION

On the basis of the available data, the CIR Panel concludes that Zinc Phenolsulfonate is safe as a cosmetic ingredient in the present practices of use and concentration.

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REFERENCES

1. ESTRIN, N.F., CROSLEY, P.A., and HAYNES, C.R. (eds.). (1982). *Cosmetic Ingredient Dictionary*, 3rd ed. Washington, D.C.: Cosmetic, Toiletry and Fragrance Assoc.
2. CTFA. (1984). Submission of unpublished data by CTFA. Cosmetic ingredient chemical description. (2-46-1).*
3. WINDHOLZ, M. (1983). *The Merck Index*. Rahway, N.J.: Merck and Co.
4. CTFA. (1985). Submission of unpublished data by CTFA. Letter dated September 19th to Dr. G.B. Vermont from H.W. Thieman (Corporate Analytical Research, Mallinckrodt, Inc.).*
5. HUNTING, A.L.L. (1983). *Encyclopedia of Shampoo Ingredients*. Cranford, N.J.: Micelle Press.
6. GOSSELIN, R.E., HODGE, H.C., SMITH, R.P., and GLEASON, M.N. (1976). *Clinical Toxicology of Commercial Products: Acute Poisoning*, 4th ed. Baltimore, Md.: Williams & Wilkins.
7. FDA. (1983). Status of ingredients in the OTC drug review.
8. WILKINSON, J.B., and MOORE, R.J. (eds.). (1982). *Harry's Cosmeticology*, 7th ed. New York: Chemical Publishing Co., Inc.
9. FOOD AND DRUG ADMINISTRATION (FDA). (1981). Computer printout of voluntary submission of cosmetic ingredient data.
10. CODE OF FEDERAL REGULATIONS (CFR). (1979). Title 21 Part 175.05, 175.320, 176.170, 176.200, 176.210, 177.1200, 177.2260, 177.2800, 178.3570, 178.3910.
11. CTFA. (1980). Submission of unpublished safety data by CTFA. Rat acute oral study. (2-46-18).*
12. CTFA. (1980). Submission of unpublished safety data by CTFA. Rat acute oral study. (2-46-19).*
13. CTFA. (1980). Submission of unpublished safety data by CTFA. Rat acute oral study. (2-46-20).*
14. CTFA. (1972). Submission of unpublished safety data by CTFA. Acute rat oral study.*

*Available upon request: Director, Cosmetic Ingredient Review, 1110 Vermont Ave., NW, Suite 810, Washington, DC 20005.

15. CTFA. (1972). Submission of unpublished safety data by CTFA. Acute mouse oral and I.P. study. (2-46-12).*
16. CTFA. (1978). Submission of unpublished safety data by CTFA. Rat acute oral study. (2-46-28).*
17. CTFA. (1978). Submission of unpublished safety data by CTFA. Rat acute oral study. (2-46-27).*
18. CTFA. (1978). Submission of unpublished safety data by CTFA. Rat acute oral study. (2-46-26).*
19. CTFA. (1973). Submission of unpublished safety data by CTFA. Rat 91-day oral study. Scientific Associates.*
20. CTFA. (1980). Submission of unpublished safety data by CTFA. Guinea pig acute dermal study. (2-46-21).*
21. CTFA. (1972). Submission of unpublished safety data by CTFA. Rabbit 28-day percutaneous study.*
22. CTFA. (1978). Submission of unpublished safety data by CTFA. Rabbit 91-day percutaneous study. International Research and Development Corp.*
23. CTFA. (1978). Submission of unpublished safety data by CTFA. Rat subchronic dermal study. (2-46-41).*
24. CTFA. (1972). Submission of unpublished safety data by CTFA. Acute rat intraperitoneal study.*
25. CTFA. (1977). Submission of unpublished safety data by CTFA. Rat acute inhalation study. (2-46-32).*
26. CTFA. (1978). Submission of unpublished safety data by CTFA. Rat acute inhalation study. (2-46-31).*
27. CTFA. (1980). Submission of unpublished safety data by CTFA. Rat acute inhalation study. (2-46-35).*
28. CTFA. (1982). Submission of unpublished safety data by CTFA. Rat acute inhalation study. (2-46-3).*
29. CTFA. (1982). Submission of unpublished safety data by CTFA. Mouse acute inhalation study. (2-46-2).*
30. CTFA. (1981). Submission of unpublished safety data by CTFA. Rat 13-week inhalation study. (2-46-36).*
31. CTFA. (1979). Submission of unpublished safety data by CTFA. Guinea pig 13-week inhalation study. Bio-Dynamics.*
32. CTFA. (1979). Submission of unpublished safety data by CTFA. Monkey 90-day inhalation study. Hazelton Laboratories America.*
33. CTFA. (1980). Submission of unpublished safety data by CTFA. Rabbit skin irritation study. (2-46-22).*
34. CTFA. (1980). Submission of unpublished safety data by CTFA. Rabbit skin irritation study. (2-46-23).*
35. CTFA. (1978). Submission of unpublished safety data by CTFA. Rabbit SIOPT study. (2-46-30).*
36. DRAIZE, J.H. (1959). In: *Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics*. Austin, Texas: The Association of Food and Drug Officials of the U.S.
37. CTFA. (1965). Submission of unpublished safety data by CTFA. Rabbit dermal irritation report. Bio/Dynamics. (2-46-15).*
38. CTFA. (1981). Submission of unpublished safety data by CTFA. Rabbit SIOPT study. (2-46-4).*
39. BUEHLER, E.V. (1965). Delayed contact hypersensitivity in the guinea pig. Arch. Derm. **91,** 171–177.
40. CTFA. (1976). Submission of unpublished safety data by CTFA. Guinea pig sensitization study. International Bio-Research.*
41. CTFA. (1984). Submission of unpublished safety data by CTFA. Rabbit eye irritation study.*
42. CTFA. (1980). Submission of unpublished safety data by CTFA. Rabbit eye irritation study. (2-46-24).*
43. CTFA. (1976). Submission of unpublished safety data by CTFA. Rabbit eye irritation study.*
44. CTFA. (1978). Submission of unpublished safety data by CTFA. Rabbit eye irritation study. (2-46-5).*
45. CTFA. (1972). Submission of unpublished safety data by CTFA. Rabbit eye irritation study, Gibraltar Biological Labs. (2-46-14).*
46. CTFA. (1964). Submission of unpublished safety data by CTFA. Rabbit eye irritation test. (2-46-13).*
47. HILL TOP RESEARCH. (1985). Submission of unpublished data by CTFA. The *Salmonella*/Microsomal Assay for Bacterial Mutagenic Activity of Zinc Phenolsulfonate.*
48. CTFA. (1978). Submission of unpublished safety data by CTFA. Clinical SIOPT study. (2-46-33).*
49. CTFA. (1980). Submission of unpublished safety data by CTFA. Clinical SIOPT study. (2-46-34).*
50. CTFA. (1977). Submission of unpublished safety data by CTFA. Clinical SIOP study. (2-46-43).*
51. CTFA. (1980). Submission of unpublished safety data by CTFA. Clinical SIOPT study. (2-46-45).*
52. PHILLIPS, L., STEINBERG, M., MAIBACH, H.I., and AKERS, W.A. (1972). A comparison of rabbit and human skin response to certain irritants. J. Tox. Appl. Pharmacol. **21,** 369–382.
53. CTFA. (1981). Submission of unpublished safety data by CTFA. Clinical cumulative irritancy study, Hill Top Research. (2-46-47).*
54. CTFA. (1979). Submission of unpublished safety data by CTFA. Clinical cumulative irritancy study. Hill Top Research. (2-46-40).*
55. CTFA. (1981). Submission of unpublished safety data by CTFA. Clinical RIPT study. (2-46-46).*
56. CTFA. (1977). Submission of unpublished safety data by CTFA. Clinical RIPT study. (2-46-42).*
57. CTFA. (1979). Submission of unpublished safety data by CTFA. Clinical RIPT study. (2-46-39).*
58. CTFA. (1980). Submission of unpublished safety data by CTFA. Clinical RIPT study. (2-46-37).*

59. CTFA. (1972). Submission of unpublished safety data by CTFA. Clinical RIPT study. Hill Top Research. (2-46-16).*
60. CTFA. (1972). Submission of unpublished safety data by CTFA. Rechallenge test of RIPT reactive panelists. Hill Top Research. (2-46-17).
61. CTFA. (1982). Submission of unpublished safety data by CTFA. Clinical RIPT study. Hill Top Research.*
62. CTFA. (1972). Submission of unpublished safety data by CTFA. Clinical RIPT study. Hill Top Research. (2-46-10).*
63. CTFA. (1978). Submission of unpublished safety data by CTFA. Clinical RIPT study. Food and Drug Research Laboratories. (2-46-6).*
64. CTFA. (1974). Submission of unpublished safety data by CTFA. Clinical RIPT study. Food and Drug Research Laboratories. (2-46-8).*
65. CTFA. (1974). Submission of unpublished safety data by CTFA. Clinical RIPT study. Food and Drug Research Laboratories. (2-46-9).*
66. CTFA. (1978). Submission of unpublished safety data by CTFA. Clinical RIPT study.*
67. CTFA. (1970). Submission of unpublished safety data by CTFA. Clinical RIPT study. Midwest Medical Evaluation. (2-46-11).*