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Final Report on the Safety Assessment of Toluenesulfonamide/ Formaldehyde Resin

Toluenesulfonamide/Formaldehyde Resin (TSFR) is used in such cosmetic products as fingernail polishes and enamels at concentrations up to 10%.

TSFR was practically nontoxic to rats when given orally as a 70% solution in acetone and when applied to the skin of rabbits as a 40% suspension in corn oil. TSFR in the form of a finely ground powder was nonirritating to rabbit skin and slightly irritating to the rabbit eye. The undiluted material was nonirritating to rabbit skin, slightly irritating to the rabbit eye, and practically nontoxic to rabbits by dermal application. No significant treatment-related effects were observed in a subchronic oral study in dogs. TSFR was negative in the Ames test for mutagenicity.

In clinical studies, 10% TSFR in dimethyl phthalate was nonirritating and nonsensitizing to the skin. Nail products containing up to 12% TSFR were nonsensitizing, nonphotosensitizing, and essentially nonirritating to the human skin. Reports of nail polish dermatitis of allergic origin have been attributed to TSFR and other liquid thermoplastic resins.

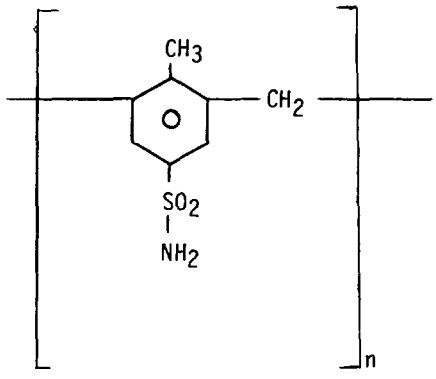
It is concluded that Toluenesulfonamide/Formaldehyde Resin (TSFR) and Toluenesulfonamide/Formaldehyde Resin-80% (TSFR-80) are safe as cosmetic ingredients in the present practices of use and concentration.

CHEMISTRY

Definition and Structure

Toluenesulfonamide/Formaldehyde Resin,* hereafter referred to as TSFR, is the polymer that conforms generally to the structure:[1]

*The safety of formaldehyde as a cosmetic ingredient has been previously reviewed.[4]



Other names for TSFR (CAS Nos.: 1338-51-8, 25035-71-6, 9008-60-0) include Santolite MHP,* Santolite MS-80 percent,* p-Toluenesulfonamide-Formaldehyde Resin, o-Toluenesulfonamide Formaldehyde Resin, Benzenesulfonamide, 4-Methyl-, Polymer with Formaldehyde, and Benzenesulfonamide, ar-Methyl-, Polymer with Formaldehyde.[2,3]

Properties

TSFR is available to cosmetic manufacturers as both a liquid and a solid. The solid form of TSFR is a hard, practically colorless material with a faint formaldehyde odor. It is soluble in alcohols, ethers, ketones, esters, and aromatic hydrocarbons. It is insoluble in aliphatic hydrocarbons and practically insoluble in water. The resin is neither a primary oxidant nor a reducing agent, and it is not reactive with water or air under ambient conditions.[2,6] Additional chemical and physical data are presented in Table 1.

TSFR-80 is a soft, viscous liquid. This solution consists of approximately 80% solids in a mixture of butyl acetate and butyl alcohol. The product is insoluble in water at 25°C, and it is miscible with all common organic solvents and thinners except aliphatic petroleum hydrocarbons. TSFR-80 is "compatible" with both nitrocellulose and cellulose acetate and forms "brittle compositions" with both of these materials; addition of a plasticizer makes such combinations permanently flexible. TSFR-80 is a combustible material. It is neither a primary oxidant nor a reducing agent and is not reactive with water or air under ambient conditions.[5,7,8] Additional chemical and physical data are presented in Table 2.

Method of Manufacture

TSFR is prepared by the condensation of aryl sulfonamides with formaldehyde.[2,9] TSFR-80 is formed by the condensation of formaldehyde with aromatic sulfonamides.[5,9] These aryl and aromatic sulfonamides were not identified.

Doviak[10] reported that when formaldehyde and p-toluene sulfonamide were employed in equimolecular proportions, they condensed to form a viscous mass, which on heating to 110°C, yielded a hard, colorless resin.

*Santolite MHP and Santolite MS-80% are registered trademarks.[5]

TABLE 1. Chemical and Physical Data for Toluenesulfonamide/Formaldehyde Resin

		Reference
Appearance	Hard, clear resin	2,6
Molecular formula	$(C_7H_9NO_2S\text{-}CH_2)_x$	3
Odor	Faint formaldehyde	6
Acid value	Approximately 1	2
Refractive index of 25 g in 75 g of butyl acetate at 25°C	1.4275–1.4325 1.430	2 6
Specific gravity at 25/25°C	1.35	2,6
Vapor pressure at 150°C	<0.1 mm Hg	6
Softening point	60°C–70°C 62°C	2 6
Flash point	171.1°C (340°F) Cleveland open cup	6
Fire point	229.4°C (445°F) Cleveland open cup	6
Viscosity at 100°C at 120°C at 140°C	 10,000 cps 880 cps 180 cps	 2,6

TABLE 2. Chemical and Physical Data for Toluenesulfonamide/Formaldehyde Resin-80%

		Reference
Appearance	Liquid (soft, viscous resin)	5,7,8
Odor	Strong butyl acetate	8
Identification	Positive; close match to a standard IR spectrum	5
Specific gravity 25°/25°C	1.23–1.24 1.256	5 8
Refractive index at 25°C	1.535–1.540	5
Vapor pressure at 25°C	~10 mm Hg	8
Viscosity at 25°C	6000–11000 cps	8
Flash point	32.2°C (90°F) (Tag closed cup and Cleveland open cup)	8
Solids[a] (100% minus % solvents)	78.8–81.2% in butyl acetate and butyl alcohol	5

[a]The various solids were not specified.

Impurities

TSFR and TSFR-80 are known to contain free formaldehyde. The formaldehyde content of TSFR-80 is <0.2%.[6,8] Data relating to other possible impurities were not available.

In a review of the safety of formaldehyde as a cosmetic ingredient, the CIR Expert Panel concluded that the concentration of formaldehyde in cosmetic products should not exceed 0.2%.[4]

NONCOSMETIC USE

TSFR and TSFR-80 are used in various indirect food contact applications. Both compounds are regulated by the U.S. Department of Agriculture as acceptable components of packaging material in contact with meat or poultry food products prepared under federal inspection.[6,8] They are also permitted as components of cellophane food packaging material (up to a limit of 0.6% by weight of the cellophane) and as components of adhesives used in food packaging articles.[11,12] Federal regulations additionally permit TSFR to be used as a side seam cement in articles intended for food contact[13] and as a component of paper and paperboard in contact with aqueous and fatty foods.[14]

TSFR-80 is also used as a solvent for nitrocellulose and cellulose acetate and in spraying, dipping, or brushing lacquers to make clear, odorless coatings.[9]

COSMETIC USE

Purpose in Cosmetics

Aryl sulfonamide-formaldehyde resins were first introduced into nail varnish films in about 1938.[15] Two commercially available resins of the aryl sulfonamide-formaldehyde type are TSFR and TSFR-80. TSFR-80 is softer and produces films of "greater flexibility" than TSFR. Both of these resins are used in nail lacquers and other nail preparations to impart high gloss and good flow properties and to increase the hardness of nitrocellulose films. They also increase the moisture resistance of nitrocellulose films, thereby reducing the incidence of water spotting and whiteness of such films.[2,15] TSFR and TSFR-80 are also employed in nail formulations to increase the flexibility and toughness of both ethyl and nitrocellulose, and "to increase the flow at elevated temperatures with polyvinyl acetate resins, imparting quick tack."[2]

Product Formulation

Data submitted to the Food and Drug Administration (FDA) in (or before) 1981 by cosmetic firms participating in the voluntary cosmetic registration program indicated that TSFR and TSFR-80 were used in a total of 211 and 356 of the registered cosmetic products, respectively (Tables 3 and 4). Product types formulated with these two resins included nail basecoats and undercoats, nail polish and enamel, and other manicuring preparations. Reported concentrations of the

TABLE 3. Product Formulation Data for Toluenesulfonamide/Formaldehyde Resin[16,17]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)				
			>10–25	>5–10	>1–5	>0.1–1	≤0.1
Nail basecoats and undercoats	44	31	–	10	21	–	–
Nail polish and enamel	767	172	1	151	11	8	1
Other manicuring preparations	50	8	–	3	5	–	–
1981 TOTALS		211	1	164	37	8	1

TABLE 4. Product Formulation Data for Toluenesulfonamide/Formaldehyde Resin-80%[16,17]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)				
			>10–25	>5–10	>1–5	>0.1–1	≤0.1
Nail basecoats and undercoats	44	5	–	4	1	–	–
Nail polish and enamel	767	344	2	227	74	32	9
Other manicuring preparations	50	7	1	2	2	–	2
1981 TOTALS		356	3	233	77	32	11

two resins in these products ranged from ≤0.1% to >10–25%, with the majority of products containing the resins in the concentration range of >5–10%.[16,17]

Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators must conform to the format of concentration ranges and product categories as described in Title 21 Part 720.4 of the Code of Federal Regulations.[18] Since certain cosmetic ingredients are supplied to the formulator at less than 100% concentration, the concentration reported by the formulator may not necessarily reflect the actual concentration found in the finished cosmetic product; the actual concentration in such an instance would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of a "concentration range" provides opportunity 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 a two- to ten-fold error in the assumed ingredient concentration.

Exposure to TSFR

The fingernail, the toenail, the nail cuticle, and the skin surrounding the nail are the areas directly exposed to TSFR and TSFR-80. However, parts of the body readily accessible to the nail may also be exposed. Such areas may include the

eye region, the face and neck, and the vulva.[19] Nail products formulated with TSFR and TSFR-80 can be applied as often as several times per week. Nail polish and enamel may typically remain in contact with the nail until removed by a solvent-based enamel remover. Cosmetics formulated with TSFR and TSFR-80 have the potential for repeated application over many years.

Typical Nail Polish Composition

The major use of TSFR and TSFR-80 is in nail polish and enamel (Tables 3 and 4). Most nail polish* formulations typically consist of the following constituents[10,19]:

1. A film former (such as ethylcellulose, nitrocellulose, cellulose acetate, cellulose acetate-butyrate, methacrylate polymers, vinyl polymers, or sucrose acetate isobutyrate)
2. Resins to improve gloss and adhesion of the film (such as TSFR)
3. Plasticizers to give the film pliability, minimize shrinkage, and soften and plasticize the film former (such as camphor or dibutyl phthalate)
4. Solvents and diluents to stabilize viscosity and to keep the film former, resin, and plasticizer in a liquid state (such as esters, glycol ethers, nitroparaffins, alcohols, xylene, or toluene)†
5. Thixotropic agents for nonsettling and flow on shaking (clay modified by quaternary ammonium compounds)
6. Coloring substances (such as fluorescent and nonfluorescent dyes, guanine, or inorganic and organic pigments)

TSFR and TSFR-80 are moderately stable to light and soluble in the majority of solvents and diluents usually employed. Because of the low viscosity of TSFR and TSFR-80 formulations, "large amounts" of these resins can be used in lacquer products without adversely affecting the ease of application of the lacquer, or the hardness or flexibility of the coating.[10,15]

Suggested formulas for various nail products containing TSFR and TSFR-80 have been described in the published literature.[10,15,20–23]

TOXICOLOGY

Acute Oral Toxicity

The acute oral toxicity of TSFR was investigated using five Sprague-Dawley albino rats (two males and three females). The test material was administered as 70.0% solution in acetone in a single 7.94 g/kg oral dose. Reduced appetite and activity were observed for 2–4 days. No animals died over a 14-day observation period, and the "viscera appeared normal" at gross examination.[24]

*The term "nail polish" is often used to denote nail enamel, nail lacquer, nail varnish, top coat, and/or basecoat.[10,15,19]

†These solvents may cause false-positive irritant reactions if not permitted to evaporate before the nail lacquer is applied under a patch to the skin.[19]

A single oral dose of 5 g/kg TSFR-80 (50% solution in "3A alcohol") was administered to five male Sprague-Dawley albino rats. Animals were subsequently observed for 14 days. Reduced activity and appetite were noted for 2–3 days. All animals survived and "viscera appeared normal" at gross examination.[25]

Three different nail polish and enamel formulations were evaluated for acute oral toxicity. The products (A, B, and C)* were tested at 100% concentration, and each was formulated with approximately 12% TSFR-80. Each product was given by stomach tube at a dose of 15.0 g/kg to five female albino rats (five rats per product). Three of the 15 rats died within 2 days following the single dose. Of the three rats that died, two died following administration of formulation A, and one died following exposure to formulation C. The surviving animals generally had normal weight gain over the 7-day observation period. The exception was a single rat that had weight loss. This animal was exposed to formulation C. The acute oral LD_{50} of each product was considered >15 g/kg.[26–28]

A nail hardener (product D) containing 8.26% TSFR-80 was evaluated for acute oral toxicity according to the procedures outlined in Title 16 Part 1500.3(b)(6)(i)(A) of the Code of Federal Regulations.[29] A single dose of 5 g/kg body weight of the wet product was given by oral intubation to each of 10 albino rats. No deaths occurred over a 14-day observation period.[30]

Ocular Irritation

TSFR (100 mg) in the form of a finely ground powder was instilled into one eye of each of six New Zealand albino rabbits. The treated eyes were not rinsed with water after exposure. Untreated eyes served as controls. Slight erythema of the conjunctivae and slight to moderate discharge were observed 1, 24, and 48 h after instillation. Ocular irritation had cleared by the 72-h evaluation. No effects on the cornea or iris were noted. The investigator concluded that the test material was a "slight" ocular irritant.[24]

The ocular irritation potential of undiluted TSFR-80 was assessed in three albino New Zealand rabbits. The test material was instilled in a single 0.1 ml dose into one eye of each rabbit. Slight erythema of the conjunctivae and ocular discharge were noted at the 1-, 24-, and 48-h evaluations. Irritation had dissipated by the 72-h evaluation. No damage to the cornea or iris was reported. It was concluded that undiluted TSFR-80 was a "slight" ocular irritant.[25]

Ocular irritation was evaluated in rabbits exposed to cosmetic formulations containing approximately 12% TSFR-80. Eighteen albino rabbits were assigned to three groups of six. Each group of six rabbits was tested with one of three different nail polish and enamel products (A, B, and C). The test material (0.1 ml) was instilled into one eye of each of the six rabbits; the untreated eye served as control. Treated eyes received no water rinse. Irritation of the cornea, iris, and conjunctivae was assessed 1, 2, 3, 4, and 7 days postinstillation according to the procedures described by Draize.[31] All 18 rabbits developed ocular irritation.

*The formulations referred to in the text as "A, B, C, D, and E" are repeatedly mentioned in this report. Thus, products A, B, C, D, and E, as discussed in this section, are the same A, B, C, D, and E as discussed in other sections of the report.

Average irritation scores (max = 110) on Days 1, 2, 3, 4, and 7 postinstillation were as follows: product A: 40, 38, 24, 14, 14; product B: 47, 37, 25, 17, 25; product C: 31, 25, 17, 12, 11. Scores of >15–25 and >25–50 were indicative of mild and moderate irritation, respectively. Corneal lesions were present throughout the observation period and were the major contributing factor to the average irritation score. On the final day of observation (Day 7), 13 of the 18 treated animals had no irritation or minimal conjunctival irritation; the remaining 5 animals had lesions of the cornea and iris. Of the 5 rabbits with injury of the cornea and/or iris on Day 7, 2 animals treated with product A had lesions, 2 exposed to product B had lesions, and 1 exposed to product C had lesions.[32–34] According to Draize,[31] "a preparation which has elicited corneal and iridial lesions which have not cleared by the seventh day is considered a severe eye irritant." It was not ascertained in this study whether or not the observed ocular irritation was a result of TSFR.

A nail hardener (product D) containing 8.26% TSFR-80 was tested for ocular irritation. The procedures outlined in Title 16 Parts 1500.3(c)(4) and 1500.42 of the Code of Federal Regulations were used to evaluate both wet and dry forms of the product.[29,35] The test material (0.1 ml or 100 mg) was instilled into one eye of each of six albino rabbits; the untreated eye served as control. Treated eyes received no water rinse following instillation of the test material. Ocular reactions were evaluated at 24, 48, and 72 h. One of six rabbits developed conjunctival erythema and chemosis, iritis, and keratitis to the dry product. All six rabbits exposed to the wet product developed iritis, conjunctival erythema, and chemosis; three of these latter six animals also had keratitis. It was not specified at which evaluation these ocular reactions were observed.[30]

Dermal Toxicity

TSFR was applied as a 40% solution/suspension in corn oil to the skin of five New Zealand albino rabbits (three males and two females). Single doses of either 2.0, 3.16, 5.01, or 7.94 g/kg were applied for 24 h. Two animals were tested at the highest dose, and one rabbit was tested at each of the other doses. Reduced appetite and activity were observed for 2–4 days. No animals died during the 14-day observation period after exposure. At gross examination, the "viscera" appeared normal.[24]

TSFR-80 was applied undiluted to the skin of three New Zealand albino rabbits. Doses of 5.01 g/kg and 7.94 g/kg were applied to one male and to one male and one female, respectively. No deaths occurred over a 14-day observation period after the single 24-h exposure. Reduced appetite and activity were observed for 2–5 days, and no lesions were found at necropsy.[25]

The procedures outlined in Title 16 Parts 1500.3(c)(1)(ii)(c) and 1500.40 of the Code of Federal Regulations were used to assess the acute dermal toxicity of a nail hardener (product D) containing 8.26% TSFR-80.[29,36] A 2 g/kg per body weight dose of the wet product was applied under an "impervious sleeve" to either the clipped skin (five rabbits) or the clipped and abraded skin (five rabbits). After 24 h, the sleeves were removed. No deaths were observed over a 2-week period.[30]

Skin Irritation

TSFR was applied as a finely ground powder (0.5 g moistened with water) under an occlusive patch to the intact and abraded clipped skin of six New Zealand albino rabbits. After 24 h, the patches were removed and the treated sites were scored for erythema and edema. Skin reactions were also evaluated 48, 72, and 168 h after the single 24-h exposure. No irritation was observed.[24]

No irritation was observed when undiluted TSFR-80 (0.5 ml) was applied for 24 h to the intact skin of three New Zealand albino rabbits. Skin erythema and edema were evaluated 4, 24, 48, 72, and 168 h after the single exposure.[25]

The skin-irritating property of three different nail polish and enamel products was assessed by means of a single insult occlusive patch test. The three formulations (A, B, and C) each contained approximately 12% TSFR-80. Each product (0.5 ml) was placed on a filter disc from which the solvents were allowed to evaporate. The filter disc was then placed in contact with the clipped skin of the back of each of nine female albino rabbits (9 rabbits per product). The filter disc was secured by means of an occlusive plastic sheet wrapped around the trunk of the animal. After 24 h, the occlusive wrappings were removed, and the test sites were scored for erythema and edema. Four of the 27 rabbits had minimal skin erythema 2 h after removal of the occlusive dressing. Of these four rabbits, one had been exposed to formulation A, one had been treated with formulation B, and two had been exposed to formulation C. One rabbit treated with formulation C had minimal skin erythema at the 24-h evaluation. All of the other treated rabbits had no irritation at the 2- or 24-h evaluations. The skin irritation potential of the three products was considered minimal.[37-39]

Skin irritation to a nail hardener (product D) containing 8.26% TSFR-80 was assessed according to the methods described in Title 16 Parts 1500.3(c)(4) and 1500.41 of the Code of Federal Regulations.[29,40] The wet product (0.5 ml) was applied for 24 h under an occlusive patch to the intact and abraded skin of each of six rabbits. Skin reactions were evaluated 24, 48, and 72 h after application. The results were not specified; however, it was reported that the product was a "nonirritant" under conditions of this test.[30]

Subchronic Toxicity

Purebred beagle dogs were given TSFR in the diet at concentrations of 0, 1000, 3000, or 10,000 ppm for 90 days. The three treatment groups and the nontreated control group each consisted of 4 male and 4 female dogs (32 animals total). No deaths were reported throughout the study. Food consumption, behavior, blood chemistry parameters, and results of urinalyses of treated dogs were comparable to those of the untreated control group. At gross and microscopic examination of tissues and organs, no treatment-related lesions were found. "Slight to moderate body weight gain suppression" was noted among females fed 10,000 ppm TSFR; males at this same dietary concentration had body weight gains "somewhat lower" than those of untreated males, "although the gains were within normal limits for dogs of this age." Body weight gains at the two lower concentrations (1000 and 3000 ppm) were comparable to those of untreated controls. Erythrocyte counts, hemoglobin concentrations, and hematocrit values

among females fed 10,000 ppm were "slightly lower than those of untreated females"; however, "the values remained within or were slightly lower than the normal range." Hematological parameters for males administered 10,000 ppm TSFR were comparable to those of untreated males; no treatment related hematological effects were noted at 1000 or 3000 ppm. "Slightly elevated" liver:body weight ratios were observed in all males and one of four females given 10,000 ppm; however, "the liver to brain weight ratios for these 5 dogs did not exceed normal limits and liver enlargement was considered minimal." "Liver weights and ratios" in the 1000 ppm and 3000 ppm treatment groups "were considered normal." Remaining organ weight data "revealed no treatment related abnormalities" at any of the concentrations tested. In this study, the following parameters were determined: (1) hematological studies: total and differential leukocyte count, erythrocyte count, hemoglobin, and hematocrit; (2) blood chemistry studies: blood urea nitrogen, serum glucose, serum alkaline phosphatase, serum glutamic-oxalacetic transaminase, serum glutamic-pyruvic transaminase, serum sodium, serum potassium, serum chloride, serum calcium, and serum magnesium; and (3) urinalyses: albumin, glucose, pH, specific gravity, and microscopic elements. Weights of the following organs were obtained: liver, kidneys, heart, brain, spleen, gonads, adrenal glands, thyroid, and pituitary gland. Microscopic examination was made of the following tissues and organs: adrenal glands, aorta, bone marrow, brain, caecum, colon, esophagus, gallbladder, gonads, heart, kidneys, liver, lungs, lymph nodes, muscle, pancreas, peripheral nerve, pituitary gland, prostate gland, salivary gland, small intestine, spinal cord, spleen, stomach, trachea, thyroid, uterus, and urinary bladder.[41]

Mutagenicity

No mutagenicity was observed when TSFR, TSFR-80, and butyl acetate were tested with and without metabolic activation in the Ames assay with five *Salmonella* strains[42] (Table 5).

TABLE 5. Results of Mutagenicity Studies[a](42)

Material tested	*Solvent*	*Metabolic activation*	*Dose*	*Result*
TSFR	DMSO	Yes	6 doses ranging from 20 to 1000 μg	Negative
TSFR	DMSO	No	7 doses ranging from 20 to 1500 μg; doses of 2000 to 3500 μg were toxic	Negative
TSFR-80	DMSO	Yes	7 doses ranging from 20 to 1500 μg; doses of 2000 to 3500 μg were toxic	Negative
TSFR-80	DMSO	No	7 doses ranging from 20 to 1500 μg; doses of 2000 to 3500 μg were toxic	Negative
Butyl acetate	As is	Yes	5 doses ranging from 1.764 to 44.1 mg; a dose of 88.2 mg was toxic	Negative
Butyl acetate	As is	No	6 doses ranging from 1.764 to 88.2 mg; doses of 132.3 to 308.7 mg were toxic	Negative

[a]*Salmonella typhimurium* indicator strains used included TA98, TA1535, TA100, TA1537, and TA1538.

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation, Sensitization, and Photosensitization

The skin irritation, sensitization, and photosensitization potential of various nail products containing 4.9–12.0% TSFR-80 were assessed in clinical studies. Results of these investigations indicated that these cosmetic products were nonsensitizing, nonphotosensitizing, and essentially nonirritating to the human skin. TSFR in dimethyl phthalate also was nonirritating and nonsensitizing. These assays are described below; results are summarized in Table 6.

A 10% w/v solution of TSFR in dimethyl phthalate was not an irritant, fatiguing agent, or sensitizer when applied to the intact and abraded skin of 50 subjects in a Shelanski Repeated Insult Patch Test. The induction phase consisted of 15 serial applications, followed 10–14 days later by a challenge application.[6,43]

A single insult occlusive patch procedure was used to evaluate the skin-irritating effects of three different nail polish and enamel products. All three products (A, B, and C) were formulated with 12% TSFR-80. Each product was placed on a Blenderm patch from which the solvents were allowed to evaporate. The patch was then applied to the forearm or upper arm of 18 panelists. The patch remained in place either 24 or 48 h. Skin responses were evaluated 2 and 24 h after patch removal. No irritation was observed in the 36 panelists treated with products A or B.[44,45] One of 18 subjects developed minimal skin erythema to product C.[46]

A nail hardener (product D) containing 8.26% TSFR-80 caused no skin irritation when applied to the nails of 51 subjects for 4 weeks in a controlled use study.[47] The areas examined included the fingernails, nailbeds, nail folds, and surrounding skin.

A modified Shelanski and Shelanski repeat insult patch test was used to determine the skin irritation and sensitization potential of a nail polish (product E) containing 4.9% TSFR-80.[55] The wet product was applied for 24 h by means of a patch every Monday, Wednesday, and Friday for a total of 10 induction applications. After a 2–3 week nontreatment period, a challenge patch was applied for 48 h. Reactions were graded according to the scoring system described by Wilkinson and Moore.[15] No skin irritation or sensitization was noted in any of the 53 panelists.[48]

Ninety-seven panelists (96 females and 1 male, aged 16–70) were tested with a nail strengthener containing 7.4% TSFR-80 for skin irritation and sensitization. Subjects with known skin diseases were excluded from the study. Approximately 0.1 ml of the product was dispensed onto a patch one-half hour before application to allow for evaporation of the volatile ingredients. Induction patches containing the test material were applied to the same site of the upper back for 24 h every Monday, Wednesday, and Friday for 3 consecutive weeks. A challenge patch was applied for 24 h to a previously untreated site on Tuesday of the sixth week. Challenge reactions were assessed 24 and 48 h after patch removal. Two subjects developed skin reactions at the treatment site during the induction phase. One of these individuals had mild erythema after the ninth induction patch. The second subject had barely perceptible to mild skin erythema after the sixth, seventh, and eighth induction patches. No skin reactions were observed to

TABLE 6. Clinical Studies with Products Containing Toluenesulfonamide/Formaldehyde Resin-80

Type of test	*Material tested*	*TSFR or TSFR-80 concentration (%)*	*No. of subjects*	*Procedure*	*Result*	*Reference*
Skin irritation/ sensitization	TSFR in dimethyl phthalate	10 (TSFR)	50	Shelanski repeat insult patch test: 15 induction applications to abraded and intact skin; after 10–14 day nontreatment period, challenge patch applied	No skin irritation or sensitization	6,43
Skin irritation	Nail polish and enamel[a] (product A)	12 (TSFR-80)	18	Single insult occlusive patch	No skin irritation	44
Skin irritation	Nail polish and enamel[a] (product B)	12 (TSFR-80)	18	Single insult occlusive patch	No skin irritation	45
Skin irritation	Nail polish and enamel[a] (product C)	12 (TSFR-80)	18	Single insult occlusive patch	One subject developed minimal skin erythema	46
Skin irritation	Nail hardener[b] (product D)	8.26 (TSFR-80)	51	Applied to nails daily for 4 weeks	No irritation of the skin surrounding the nails	47
Skin irritation/ sensitization	Nail polish[b] (product E)	4.9 (TSFR-80)	53	Modified Shelanski and Shelanski repeat insult patch test: product applied to skin by 24-h patch every Mon., Wed., Fri. for 3 weeks; after 2–3 week nontreatment period, 48-h challenge patch applied	No skin irritation or sensitization	48
Skin irritation/ sensitization	Nail strengthener[a]	7.4 (TSFR-80)	97	Repeat insult patch test: product applied to skin every Mon., Wed., Fri. for 3 weeks; after 2 week nontreatment period, 24-h challenge patch applied	Two subjects developed mild skin erythema during induction phase; no sensitization reactions observed	49

Skin irritation/ sensitization	Nail color[a]	6.5 (TSFR-80)	148	Draize-Shelanski-Jordan repeat insult patch test: product applied to skin every Mon., Wed., Fri. for 3 weeks; after 2 week nontreatment period, 2 consecutive 48-h challenge patches applied	No skin irritation or sensitization	50
Skin irritation/ sensitization	Nail color[a]	9.0 (TSFR-80)	203	Draize-Shelanski-Jordan repeat insult patch test: product applied to skin every Mon., Wed., Fri. for 3 weeks; after 2 week nontreatment period, 2 consecutive 48-h challenge patches applied	One subject developed faint skin erythema during induction phase; no skin sensitization observed	51
Skin irritation/ sensitization/ photosensitization	Nail polish[b] (product E)	4.9 (TSFR-80)	101	Schwartz and Peck[52] with UV exposure: For induction phase, set of open and closed patches applied to skin for 48 h; after 10 day nontreatment period, open and closed challenge patches applied for 48 h; treated sites exposed to UV irradiation during induction and challenge phases	One subject developed weak nonvesicular reaction to closed patch during induction phase; no other irritation, sensitization, or photosensitization reactions observed	48
Phototoxicity/ photosensitization	Nail color[c]	9.0 (TSFR-80)	30	Exposure to product and UV irradation repeated twice weekly for 3 weeks for a total of 6 induction treatments; after 10-day nontreatment period, product was applied under occlusion to previously untreated site; challenge site irradiated with UV light for 3 minutes	No phototoxic or photoallergic skin reactions observed	53

TABLE 6. (Continued)

Type of test	*Material tested*	*TSFR or TSFR-80 concentration (%)*	*No. of subjects*	*Procedure*	*Result*	*Reference*
Phototoxicity/ photosensitization	Nail color[c]	9.0 (TSFR-80)	28	Exposure to product and UV irradiation repeated twice weekly for 3 weeks for a total of 6 induction treatments; after 10-day nontreatment period, product was applied under occlusion to previously untreated site; challenge site irradiated with UV light for 3 minutes	No phototoxic or photoallergic skin reactions observed	54

[a]Test material was applied dry, i.e., solvents were allowed to evaporate prior to application.
[b]Test material was applied wet, i.e., solvents were not allowed to evaporate prior to application.
[c]Not specified whether or not solvents were allowed to evaporate prior to application.

the single challenge patch. It was concluded that the nail strengthener "did not exhibit any potential for inducing allergic sensitization."[49]

A Draize-Shelanski-Jordan repeat insult patch test was conducted to evaluate the skin irritation and sensitization potential of two different nail color products. One formulation contained 6.5% TSFR-80 and was evaluated on 148 subjects (89 females, 59 males).[50] The second nail product contained 9.0% TSFR-80 and was evaluated on 203 subjects (144 females, 59 males).[51] All panelists were between the ages of 18 and 65. Only subjects with no known skin diseases or allergies were selected for testing. Impermeable dry patches containing the test material were applied to the upper back on Monday, Wednesday, and Friday for 3 consecutive weeks for a total of nine induction exposures. After a 2-week nontreatment period, two consecutive 48-h challenge patches were applied to sites adjacent to the original induction site. Skin responses were scored on a scale of 0 (no reaction) to 4 (bullae or extensive erosion). The product containing 6.5% TSFR-80 produced "no significant reactions" during the induction phase. One subject developed a single 1+ reaction (macular, faint erythema involving 25% of the test area) during the induction phase to the product containing 9.0% TSFR-80. No skin sensitization was observed to either nail color product.[50,51]

One hundred one panelists were exposed in a modified Schwartz-Peck prophetic patch test to a nail polish (product E) containing 4.9% TSFR-80.[52] For the induction phase, a set of open and closed patches containing the wet product was applied for 48 h to the skin. Ten days after the induction exposure, a similar set of open and closed challenge patches was applied. The treated sites were exposed to UV irradiation during both induction and challenge phases. Skin reactions were evaluated according to the grading system described by Wilkinson et al.[56] One subject developed a weak, nonvesicular skin reaction to the closed induction patch. No other irritation, sensitization, or photoreactions were observed.[48] Test methodology for the UV exposure was not reported.

No phototoxicity or photosensitization was observed in groups of 30 or 28 human subjects exposed to UV irradiation and two nail color products each containing 9% TSFR-80. Before testing, the minimal erythemal dose (MED) of each panelist was determined in accordance with the procedures outlined in the Federal Register.[57] Occlusive patches containing the test material were applied to the back for 24 h (0.1 ml/cm^2). Upon removal of the patch, the site was irradiated with three times the individual's MED using a Xenon Arc Solar Simulator (150 W). The lamp was filtered to produce a continuous spectrum in the UVA and UVB region (290–400 nm). Forty-eight hours after UV exposure, the treated sites were scored for erythema, edema, and vesicular skin reactions. Exposure to product and UV irradiation was repeated twice weekly for 3 weeks for a total of six induction treatments. Following a 10-day nontreatment period, an occlusive patch containing the test material was applied for 24 h to a previously untreated site adjacent to the induction site. After removal of the patch, the challenge site was irradiated for 3 minutes. In this instance, a Schott WG 345 glass filter was placed over the lamp to remove UVB light. Challenge responses were evaluated 15 minutes, 24 h, 48 h, and 72 h postirradiation. No phototoxic or photoallergic reactions were detected in either of the two groups.[53,54] It was not specified whether or not the solvents of the two nail colors were allowed to evaporate before testing.

Nail Polish Dermatitis

Nail polish dermatitis of allergic origin rarely occurs in the region of the fingernails or toenails but occurs instead on parts of the body accessible to the nails. Four areas typically involved in nail polish dermatitis are the eyelids, the lower half of the face, the sides of the neck, and the upper chest. Areas less frequently involved are the bridge of the nose, forehead, retroauricular zone, shoulder, and vulva. Sometimes, widespread areas may be involved, resulting in generalized dermatitis.[19] Because dermatitis occurs most frequently at distant sites that come in contact with the moist nail lacquer, Fisher[58] described nail lacquer dermatitis as an "ectopic" dermatitis.

Although any ingredient in the nail polish may account for "distant allergic eczematous contact dermatitis," liquid TSFR and other thermoplastic resins are considered the primary causative agents.[19,59] According to Fisher,[59] TSFR is the most common cause of nail polish dermatitis, whereas the film formers (usually nitrocellulose), plasticizers, solvents, and coloring agents in nail enamels are only rarely the cause of allergic contact dermatitis. Many nail enamels contain synthetic resins that are applied in a "partially polymerized liquid state."[59] Fisher[58,59] and Baran[19] claim that as TSFR-80 and other liquid thermoplastic resins dry, they become less sensitizing to the skin, and when completely dry, these resins are only very weak allergens. Fisher[58,59] suggests that individuals who are allergic to a nail polish can use that same polish provided the fingers do not contact the skin until the product has dried.

Case Reports

Wilkinson and Moore[15] reported that some nail lacquer users develop a skin sensitivity to aryl sulfonamide-formaldehyde resins. It was suggested that such persons use a nail varnish that does not include these resins.

Three women who acquired a dermatitis of the neck, face, and/or eyelids from various nail lacquers containing TSFR were studied. All three patients had positive patch test reactions to nail lacquers and to TSFR.[58]

Patients identified as "contact dermatitis cases" were patch tested with various cosmetic materials. Patches containing the materials were applied to the upper back for 48 h. Sixteen of the 8093 patients tested developed "cutaneous reactions" to TSFR. The concentration of TSFR and the test vehicle were not specified.[60]

Two women developed onycholysis of the fingernails following use of a hardener and polish containing TSFR. Both patients were patch tested with a standard patch test tray and to the nail hardener and polish. In both subjects, a "2+ reaction" was observed to the nail hardeners, TSFR, and 2% formaldehyde in petrolatum. Two months after discontinuance of the use of nail hardeners, all nails had regrowth and were "almost normal" in appearance.[61] The authors suspected that one of the nail products was the cause of the onycholysis.

Brauer[62] reported a number of deficiencies in the previous report by Paltzik and Enscoe.[61] He suggested that Paltzik and Enscoe did not prove "instances of onycholysis resulting from toluene sulfonamide/formaldehyde-containing products."

SUMMARY

Toluenesulfonamide/Formaldehyde Resin (TSFR) is available to cosmetic manufacturers in liquid (80% "solids" in a mixture of butyl acetate and butyl alcohol) and solid forms. It is prepared by the condensation of aryl or aromatic sulfonamides with formaldehyde.

TSFR has several indirect food additive uses. It is used as a "side seam cement" for articles intended for food contact, as a component of paper and paperboard in contact with food, and as a component of cellophane packaging material intended for food contact. TSFR-80 is used as a solvent for nitrocellulose and cellulose acetate and is used in lacquers to make clear coatings.

TSFR and TSFR-80 are used in such cosmetic products as nail basecoats and undercoats, nail polish and enamel, and other manicuring preparations. They impart high gloss, moisture resistance, and flow characteristics to these products, as well as increase the hardness of nitrocellulose and ethyl cellulose films. Data submitted to the FDA in 1981 under the voluntary cosmetic registration program indicated that TSFR and TSFR-80% were used in approximately 567 of the registered nail products. The majority of formulations contained this resin in the concentration range of > 5 to 10%.

The fingernail, toenail, nail cuticle, and skin surrounding the nail are the areas directly exposed to cosmetics containing TSFR and TSFR-80. The wet nail may also come in contact with such areas as the eye region, the face, the neck, and the vulva.

In acute studies, TSFR was practically nontoxic to rats when given orally as a 70% solution in acetone and was practically nontoxic to rabbits when applied to the skin as a 40% suspension in corn oil. TSFR in the form of a finely ground powder was nonirritating to rabbit skin and slightly irritating to the rabbit eye. No significant treatment-related effects were observed in a subchronic oral study in which beagle dogs were administered 1000, 3000, or 10,000 ppm TSFR. TSFR was nonmutagenic in the Ames assay.

In acute studies with TSFR-80, the undiluted material was nonirritating to rabbit skin, slightly irritating to the rabbit eye, and practically nontoxic to rabbits by dermal application. TSFR-80 also was practically nontoxic to rats when given orally as a 50% solution in alcohol. Nail polish and enamel formulations containing approximately 12% TSFR-80 were nontoxic to rats by oral administration, severely irritating to the rabbit eye, and minimally irritating to rabbit skin. TSFR-80 was negative in the Ames test for mutagenicity.

In clinical studies, 10% TSFR in dimethyl phthalate was nonirritating and nonsensitizing to the skin. Nail products containing approximately 4.9–12.0% TSFR-80 were nonsensitizing, nonphotosensitizing, and essentially nonirritating to the human skin.

Reports in the literature suggest that nail polish dermatitis of allergic origin rarely occurs in the region of the fingernails or toenails but rather on parts of the body accessible to the nails. Because dermatitis occurs most frequently at sites that come in contact with the wet nail lacquer, nail lacquer dermatitis is referred to as an "ectopic" dermatitis.

Although any ingredient in the nail polish may account for allergic contact dermatitis, it is reported that TSFR-80 and other liquid thermoplastic resins are

the probable primary causative agents. These resins are applied to the nail in a partially polymerized liquid state. It is claimed that as these resins dry, they become less sensitizing to the skin. When completely dry, they are purported to be only very weak allergens.

DISCUSSION

Although the clinical data were limited to studies with products, it is the Panel's opinion that the combined animal and clinical data were sufficient to assess the safety of TSFR and TSFR-80.

CONCLUSION

On the basis of the available data, the CIR Panel concludes that Toluenesulfonamide/Formaldehyde Resin (TSFR) and Toluenesulfonamide/Formaldehyde Resin-80% (TSFR-80) are safe as cosmetic ingredients in the present practices of use and concentration.

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