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Final Report on the Safety Assessment of Ammonium and Glyceryl Thioglycolates and Thioglycolic Acid

Ammonium and Glyceryl Thioglycolates and Thioglycolic Acid are used predominantly in cosmetic permanent waving lotions at concentrations up to 15.4% (as Thioglycolic Acid). At use concentrations, these cosmetic ingredients are only slightly toxic in acute single oral and dermal exposures. In repeated dermal tests for extended periods of exposure, these ingredients were toxic. Commercial permanent wave products produced transient conjunctival redness to both rinsed and unrinsed eyes.

The results of skin testing for irritation and sensitization of these Thioglycolates depends on the type of test system used. Under occlusive patch testing, the data indicate that these ingredients are cumulative irritants and possibly weak sensitizers, but not under semi-occlusive test conditions. In clinical patients, mainly hairdressers, Glyceryl Thioglycolate elicited allergic reactions at concentrations down to 0.25%. It is concluded that these cosmetic ingredients may be safely used at infrequent intervals. However, hairdressers should avoid skin contact.

CHEMISTRY

Chemical and Physical Properties

AMMONIUM THIOGLYCOLATE (CAS No. 5421-46-5) is the ammonium salt of Thioglycolic Acid that conforms to the formula[1]:

$$HSCH_2COONH_4$$

Ammonium mercaptoacetate and mercaptoacetic acid, monoammonium salt, are other names for this chemical.[1] Ammonium Thioglycolate evolves hydrogen sulfide.[2,3] The ultraviolet absorbance of Ammonium Thioglycolate (containing 59.7% Thioglycolic Acid in water) and its 1:100 and 1:2000 dilutions was evaluated. Except for what appeared to have been a shoulder at 320 to 340 nm (spectrum of undiluted sample), no maxima were observed above 260 nm.[4] Additional properties of Ammonium Thioglycolate are listed in Table 1.

TABLE 1. PROPERTIES OF AMMONIUM THIOGLYCOLATE, THIOGLYCOLIC ACID, AND GLYCERYL THIOGLYCOLATE

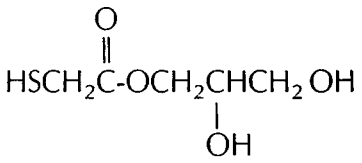
Property	*Ammonium Thioglycolate*	*Thioglycolic Acid*	*Glyceryl Thioglycolate*
Molecular weight	109.13[6]	92.12[6]	166.15[6]
Form	Slightly pink aqueous solution[6]	Colorless liquid[6]	Colorless liquid[6]
Odor	Repulsive[2]	Pungent[6]	Typical of esters[6]
Boiling point		101.5°C[6]	300°C[6]
Freezing point		−16.5°C[6]	
Specific gravity		1.325[6]	1.32[6]
Refractive index (20°C)			1.4618[6]
pH	5.5–6.8[6]		
Miscibility/solubility	Miscible with water and ethanol; immiscible with acetone, benzene, chloroform, and ether[7]	Miscible with acetone, ethanol, and water[7]	Miscible with water[8]
UV spectrum	λ_{max} = 260 nm[4]		λ_{max} = 233.8 nm[9]

Thioglycolic Acid* (CAS No. 68-11-1) is an organic acid that conforms generally to the formula[1]:

$$HSCH_2COOH$$

Other names for this chemical include: thioglycollic acid, mercaptoacetic acid, 2-mercaptoethanoic acid, and thiovanic acid.[1,3,5] Properties of Thioglycolic Acid are listed in Table 1.

Glyceryl Thioglycolate is the monoester of glycerin and Thioglycolic Acid that conforms generally to the formula[1]:



Glycerol monomercaptoacetate and glyceryl monothioglycolate are other names for Glyceryl Thioglycolate.[1] The maximum ultraviolet absorbance of Glyceryl Thioglycolate (750 mg/ml in acetonitrile) was observed at approximately 233.8 nm.[9] Additional properties of this ingredient are listed in Table 1.

In cosmetics, Thioglycolic Acid is always present as an anion ($HS—CH_2—COO^-$ or $^-S—CH_2—COO^-$). The active species in the process of hair waving is the dianion. Glyceryl Thioglycolate is present in cosmetics in the form of either $G—OCO—CH_2S^-$ or $G—OCO—CH_2—SH$. Current thinking on transdermal penetration would identify Glyceryl Thioglycolate as the more significant skin penetrant. Upon skin penetration, the mercaptide of Thioglycolic Acid is neutralized to the mercaptan ($HS\text{-}CH_2—COO^-$).

*Thioglycolic Acid salts, but not free Thioglycolic Acid, are used in cosmetic products.

The mercaptide of Glyceryl Thioglycolate, G—OCO—CH_2S^-, can exist in body fluids at physiological pH.[10]

Methods of Production

Ammonium Thioglycolate may be prepared by mixing Thioglycolic Acid with aqueous ammonia.[6]

Thioglycolic Acid may be prepared via the reaction of sodium or potassium chloracetate with alkali metal hydrosulfide in aqueous medium. The reaction mixture is acidified and purified by organic extraction and vacuum distillation.[6]

Glyceryl Thioglycolate is prepared via esterification of a mixture of glycerin and Thioglycolic Acid.[6] The result is a complex mixture of the alpha and beta monoester, diesters (1,2 and 1,3), and triester. Unreacted Thioglycolic Acid, water, glycerin, and dithioglycolate species, from oxidation of the thiol reactant and products, also are present.[11]

Reactivity

Ammonium Thioglycolate is air oxidized to disulfide salts.[6]

Thioglycolic Acid reacts with molecular oxygen to form dithiodiglycolic acid.[12] It also is readily oxidized by ozone.[13] In aqueous solution, Thioglycolic Acid reacts with diethyl acetylmalonate to form acetylmercaptoacetic acid and diethyl malonate.[14] Additionally, it serves as a reducing agent in the conversion of Fe(III) to Fe(II).[15]

Glyceryl Thioglycolate is air oxidized.[6]

Analytical Methods

Thioglycolic Acid has been identified via the following methods: potentiometric titration with silver nitrate solution,[16] thin-layer chromatography,[17] high pressure liquid chromatography,[18] reversed-phase ion-pair high-performance liquid chromatography,[19] gas chromatography,[20] and high-performance liquid chromatography.[21]

Impurities

Ammonium Thioglycolate consists of Ammonium Thioglycolate (60%) and dithiodiglycolate (2% maximum).[6] The following are listed in the CTFA Specification for Ammonium Thioglycolate: Thioglycolic Acid (between 50% and 60%), sulfated ash (0.05% maximum), arsenic (3 ppm maximum), copper (1 ppm maximum), iron (1 ppm maximum), and lead (20 ppm maximum).[7]

Thioglycolic Acid consists of Thioglycolic Acid (78% minimum), iron (0.02 ppm maximum), and monochloroacetic acid (0.05% maximum).[6] The following are listed in the CTFA Specification for Thioglycolic Acid: dithiodiglycolic acid (2.0% maximum), sulfated ash (0.05% maximum), arsenic (3 ppm maximum), copper (1 ppm maximum), and lead (20 ppm maximum).[7]

Glyceryl Thioglycolate consists of Glyceryl Thioglycolate (80% ± 2%) and Thioglycolic Acid (2% maximum),[6] as well as glycerin and traces of dithioglycolate species.[11]

USE

Purpose in Cosmetics

Ammonium Thioglycolate and Glyceryl Thioglycolate are used in permanent wave and hair straightening preparations. Ammonium Thioglycolate also may be used in permanent hair colors, levels up to 0.25%, as a stabilizer against oxidation.[11] Thioglycolic Acid is used in permanent wave preparations, depilatories, and hair straighteners, usually in the form of ammonium, sodium, or calcium salts.[6] Thioglycolates reduce the cystine disulfide linkages in the hair cortex, thereby weakening the keratin molecule.[22,23]

Scope and Extent of Use in Cosmetics

The FDA cosmetic product formulation computer printout[24] is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[25] Ingredients are listed in preset 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 would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provide the 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 the possibility of a two- to ten-fold error in the assumed ingredient concentration. The product formulation listings for Ammonium Thioglycolate, Thioglycolic Acid, and Glyceryl Thioglycolate appear in Table 2.

Manufacturers frequently order commercial Glyceryl Thioglycolate based on a specific thioester specification (up to 80.0%) and thioacid specification (up to 2.0%). For use in permanent wave products, it is supplied as a separate component to be mixed, at the time of use, with an aqueous alkaline buffered solution. This brings the actual waving solution pH to between 6.0 and 8.5. Although the concentration of Glyceryl Thioglycolate, as supplied, is often expressed as 80.0% active, the use concentration in permanent wave products is less than 20.0% because of dilution upon mixture with the buffered solution before use. Thus, use concentrations of $> 50.0\%$ Glyceryl Thioglycolate (14 products, Table 2) probably represent its concentrations prior to mixture with a buffered solution.[11]

The following concentrations of Thioglycolic Acid and its salts and esters are permitted in cosmetics used in countries of the European Economic Community (EEC): depilatories (5%), hair waving or straightening products for general use (8%), hair waving or straightening products for professional use (11%), and other hair care products that are removed after application (2%).[26] Thioglycolic Acid and its salts and esters are not included in the list of cosmetic ingredients permitted for use in Japan.[27]

Surfaces to Which Applied

Cosmetic products containing Ammonium Thioglycolate, Thioglycolic Acid, Glyceryl Thioglycolate, or Sodium Thioglycolate are applied commonly to the face, legs, and hair and may come in contact with the scalp and ocular and nasal mucosae.

TABLE 2. PRODUCT FORMULATION DATA[24]

Product category	Total No. of formulations in category	Total No. containing ingredient	No. of product formulations within each concentration Range (%)					
			>50[a]	>25-50	>10-25	>5-10	>1-5	>0.1-1
Ammonium Thioglycolate								
Hair straighteners	64	5		1	—	4	—	—
Permanent waves	501	175		8	55	65	39	8
1989 Totals		180		9	55	69	39	8
Thioglycolic Acid								
Hair straighteners and permanent waves	1383	38		1	22	11	4	—
Hair dyes and colors and other hair care products	1328	12		—	3	2	—	7
Depilatories	29	6		—	—	2	4	—
1989 Totals		56		1	25	15	8	7
Glyceryl Thioglycolate								
Permanent waves	485	17	14	2	—	—	1	—
1989 Totals		17	14	2	—	—	1	—

[a]Glyceryl Thioglycolate concentrations prior to mixture with a buffered solution.

Duration of Application

Cold wave products containing Ammonium Thioglycolate may be expected to remain on the skin or hair for as long as 10 to 40 min.[28] Although permanent waves generally will process in 30 min, in actual practice, they may remain on the head for up to 1 h.[11]

Noncosmetic Use

Thioglycolic Acid (mercaptoacetic acid) is used in the manufacture of thioglycolates and pharmaceuticals. It is also a vinyl stabilizer and reagent for iron.[2,15] A stabilizer for vinyl chloride plastics, formed from the reaction of C_{10-16} alkyl mercaptoacetates with dichlorodioctylstannane and trichlorooctylstannane, is safe for use as an indirect food additive.[29]

The threshold limit value (TLV) for cutaneous exposure to Thioglycolic Acid is 4 mg/cm^3 of air. This value represents the time-weighted average concentration, for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be exposed repeatedly without adverse effect.[30]

BIOLOGICAL PROPERTIES

The following effects of Thioglycolic Acid have been reported: potentiation of bradykinin-induced contractions of guinea pig gut and uterus,[31] inactivation of hypocalcemic activity of the salivary gland hormone, β-parotin,[32] stimulation of guinea pig skin histidase activity,[33] inhibition of thyroid iodinating enzyme system (in calf thyroid) in the presence of a hydrogen peroxide-generating system,[34] inhibition of uterine response to oxytocin in rats,[35,36] diabetogenic effect in rats,[37] reduction of rat hepatic succinoxidase activity.[38,39] reduction of bovine antidiuretic factor activity,[40] and inhibition of fatty acid oxidation.[41–45]

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

The absorption of ^{35}S-Sodium Thioglycolate was investigated using male rabbits (2–3 kg, strain not stated). Five animals were fed during a period of approximately 24 h and then fasted for 24 h. A 25.0% solution of ^{35}S-Thioglycolic Acid (330 mg/kg) was then applied to clipped skin of the back via inunction. At the end of 1 h, 5 to 8% of the dose of ^{35}S-Thioglycolic Acid applied had been excreted in the urine. The amount excreted at 5 h varied from 30% to 40%. The increased excretion of ^{35}S per unit time may not have been attributable directly to percutaneous Thioglycolate absorption because Sodium Thioglycolate may have altered the metabolism of other sources of sulfur in the body. No further increase in the absorption and excretion of Thioglycolate per unit time was observed when a larger dose of the test solution (660 mg/kg) was applied to three additional rabbits (same procedure). Animals receiving the 660 mg/kg dose died (cause of death not stated) within 24 h, whereas none of the animals in the 330 mg/kg dose group died. Hence, the total amount absorbed over an extended period of time probably was related to the amount applied.[46]

The distribution of radioactivity in a female monkey (weight = 6 kg) was determined after intravenous injection of ^{35}S-Sodium Thioglycolate (3 mg/kg). Urine was collected up to 10 h postinjection, at which time the animal died. Samples of blood and urine were analyzed for ^{35}S content. Two tissue samples from each of the following organs also were analyzed for ^{35}S content: soleus muscle, kidneys, lungs, liver, heart, spleen, pancreas, and brain. The greater counts of radioactivity were found in the kidneys, lungs, and spleen.[46]

In another study, the distribution of radioactivity in Holtzman rats (weights = 200–250 g) and in an adult New Zealand rabbit (weight not stated) was determined after intravenous injection of ^{35}S-Thioglycolic Acid. One rat was intravenously injected with 50 mg/kg of the test substance and killed 1 h later. Radioactivity was greatest in the small intestine and kidneys, less in the liver and stomach, and least in the brain, heart, lungs, spleen, testes, muscle, skin, and bone. The greatest content of ^{35}S, 0.66% of the total administered was detected in the feces. This observation may have been due to contamination of the feces with urine missed during the rinsing of urine residue from the cage after collection. The distribution of ^{35}S in whole blood was evaluated in six rats injected intravenously with 100 mg/kg of the test substance and bled during periods of up to 7 h. Residual ^{35}S blood concentrations during 0.5 to 7 h postinjection did not exceed 5.3% in any of the six animals. The distribution of ^{35}S-Thioglycolic Acid in the blood was further investigated in the New Zealand rabbit, with emphasis on binding to the following serum protein fractions: α_1, α_2, β, and γ-globulins and albumin. The test substance (70 mg/kg) was injected intravenously. Most of the radioactivity was bound to albumin. The extent of this uptake amounted to 0.14% at 20 min postinjection and had diminished to 0.016% at 3 h. The small amount of radioactivity detected in albumin might have been due to isotopic exchange.[47]

The metabolism and excretion of ^{35}S-Thioglycolic Acid were evaluated in male Holtzman rats (weight = 200–250 g) and in adult male New Zealand rabbits (weights not stated). The test substance (100 mg/kg) was administered to 12 rats via intravenous injection and to 10 rats via intraperitoneal injection. Also, 2 rats were each given a dose of 75 mg/kg via intraperitoneal injection. Animals injected intravenously (12 rats) comprised one group, and those injected intraperitoneally (12 rats) comprised the other. Urine samples samples were collected 24 h after injection, after which percentages of administered ^{35}S excreted were determined. The mean urine sulfate content for intravenously injected rats was 82.3 ± 1.6% and for intraperitoneally injected rats was 90.6 ± 1.8%. Most of the radioactivity was excreted in the form of neutral sulfate. Two rabbits were injected intraperitoneally with 100 mg/kg of the test substance, and one rabbit was injected with 200 mg/kg. Urine samples were collected 24 h after injection. The mean urine sulfur content (three rabbits) was 88% of the administered dose. As was true for rats, most of the radioactivity was excreted in the form of neutral sulfate. Additionally, Thioglycolic Acid (100–150 mg/kg, no radioactivity) was administered to a group of seven rabbits via intraperitoneal injection. Significant concentrations of dithioglycolate (average concentration 28%) were detected in the urine of 24 h postinjection. Only negligible concentrations of Thioglycolate were detected.[47]

The urinary excretion of Sodium Thioglycolate was evaluated using rabbits (weights and strain not stated). Four animals were injected intravenously with a 5% solution of radioactive Sodium Thioglycolate (doses of 70, 80, 80, and 123 mg/kg, respectively). Two animals served as controls. Urine was then collected over a period of 24 h. A few drops of liquid petrolatum were placed in each container to prevent air oxidation of

possible sulfhydryl compounds. Quantities of organic sulfate, inorganic sulfate, and neutral sulfur in each urine sample were expressed as the percentage of administered radioactivity. Results indicated that Sodium Thioglycolate was excreted mostly as inorganic sulfate and neutral sulfur.[48] The urinary excretion of Sodium Thioglycolate was evaluated also in rats (weight and strain not stated) injected intraperitoneally with 12.5 to 75.0 mg/kg of a 2.5% solution of radioactive Sodium Thioglycolate. Urine was collected over a period of 24 h. Quantities of inorganic sulfate excreted, expressed as % of administered radioactivity, ranged from 29% to 72%.[48]

In another study, the urinary excretion of Ammonium and Sodium Thioglycolate mixtures was evaluated in rabbits (2.3–3.0 kg, strain not stated). The lotions (L) tested were as follows: L-1 (0.6 N Ammonium Thioglycolate, pH 9.3), L-5 (0.6 N Ammonium Thioglycolate with 0.5% active benzalkonium chloride, pH 9.3), L-15 (0.6 N Ammonium Thioglycolate with 4.0% benzalkonium chloride, pH 9.3), L-3 (0.6 N Ammonium Thioglycolate with 0.5% sodium oleate, pH 9.3), L-7 (0.6 N Ammonium Thioglycolate with 1.0% sodium salt of alkyl aryl polyether sulfonate, pH 8.6), L-14 (0.6 N Ammonium Thioglycolate with 4.0% sodium salt of alkyl aryl polyether sulfonate), and L-19 (0.6 N Sodium Thioglycolate with 4.0% sodium salt of alkyl aryl polyether sulfonate, pH 9.3). A single application (1.0 ml/kg) of each lotion was made via a syringe to a clipped area (15% of body surface) on an animal's right side. All lotions contained 10 to 20 μCi of ^{35}S. The greatest percentage of ^{35}S excreted in the urine (22.10 ± 0.94%, 7 animals) was noted 24 h after application of L-15. The smallest percentage of ^{35}S excreted at 24 h (7.72 ± 1.07%, 5 animals) resulted after the application of L-3. Seventy-two hours after administration of L-15 and L-3, the percentages of ^{35}S excreted in the urine were 2.00 ± 0.13% (4 animals) and 1.07 ± 0.35 (5 animals), respectively. When the lotions were applied daily (1.0 ml/kg) for 4 days, the greatest urinary excretion of ^{35}S occurred after the application of L-15 (approximately 60% at the end of day 4).[49]

Small quantities of Thioglycolic Acid, as cysteine-thioglycolic acid mixed disulfide, have been identified in human urine via high voltage paper electrophoresis.[50]

The pulmonary excretion of Sodium Thioglycolate as hydrogen sulfide was investigated in the rat (weight and strain not stated). The animal was injected intraperitoneally with 150 mg/kg of Sodium Thioglycolate. Expired air from the animal was analyzed for hydrogen sulfide over a period of 10 h. Hydrogen sulfide was not detected in expired air at any time during the study.[48]

TOXICOLOGY

Acute Inhalation Toxicity

Ammonium Thioglycolate

The acute inhalation toxicity of a liquid droplet aerosol containing aqueous Ammonium Thioglycolate (60% Thioglycolic Acid) was evaluated using rats (number and strain not stated). Animals were exposed to the aerosol for 1 h and then observed for 14 days. The LC_{50} was greater than 2.75 mg/L. None of the animals died. Few animals experienced respiratory distress, and signs were not observed beyond 24 h postexposure. At necropsy, minor pulmonary abnormalities were observed.[51]

Acute Oral Toxicity

In rats dosed with Glyceryl Thioglycolate, the LD_{50} was between 0.1 and 0.5 ml/kg.[52] Also in rats, a dose of 1 g/kg of an acid wave formulation that contained 19.9 to 22.0% Glyceryl Thioglycolate was below the LD_{50}.[53] Similar results were reported after rats were dosed with 1 g/kg of a cold wave formulation that contained 17.5% Ammonium Thioglycolate.[54] Studies on pure Ammonium Thioglycolate were not available. Additional oral toxicity studies are summarized in Table 3.

Short-Term Oral Toxicity

Ammonium Thioglycolate

No signs of toxicity were noted in dogs (average weight = 11.0 kg) that were fed 2.0 g of Ammonium Thioglycolate over a period of 2 days. Vomiting resulted when the dose was increased to 5.0 g.[55]

Acute Intraperitoneal and Intravenous Toxicity

Acute intraperitoneal and intravenous toxicity studies of Thioglycolic Acid and its Ammonium and Sodium salts are summarized in Table 4.

TABLE 3. ACUTE ORAL TOXICITY

Test substance	*No. of animals*	*Procedure*	*Results*	*Reference*
Cold wave (17.5% Ammonium Thioglycolate)	10 albino rats (208-260 g)	Oral dose	LD_{50} >1 g/kg	54
Permanent waving solution (10.98% Ammonium Thioglycolate)	30 Sprague-Dawley rats (200-300 g)	Intubation	LD_{50} = 1.8 ± 0.2 ml/kg	56
Permanent waving solution (7.1% Ammonium Thioglycolate)	30 Sprague-Dawley rats (200-300 g)	Intubation	LD_{50} = 2.25 ± 0.2 ml/kg	57
Permanent waving solution (7% Ammonium Thioglycolate)	70 Sprague-Dawley rats (200-296 g)	Intubation	LD_{50} = between 3.0 and 3.5 g/kg	58
Glyceryl Thioglycolate	Groups of 4 rats (99-120 g)	Intubation	LD_{50} between 0.1 and 0.5 ml/kg	52
Acid wave (22% Glyceryl Thioglycolate)	26 Crl: COBS albino rats (150-238g)	Intubation	LD_{50} = 1102 ± 59.78 mg/kg	59
Acid wave (19.9-22.0% Glyceryl Thioglycolate)	10 albino rats (216-286 g)	Oral dose	LD_{50} >1 g/kg	53
Exothermic Acid Wave (21% Glyceryl Thioglycolate)	10 Wistar albino rats (200-300 g)	Oral dose	LD_{50} <5 g/kg	60
Glyceryl Thioglycolate (3.75% in water)	50 Spf rats	Oral dose	LD_{50} = 172 mg/kg	61
Sodium Thioglycolate (5%)	10 CAF_1 mice (15-24 g)	Oral dose	LD_{50} = 504 ± 31 mg/kg	46

TABLE 4. ACUTE INTRAPERITONEAL AND INTRAVENOUS TOXICITY

Test substance	*No. of animals*	*Procedure*	*Results*	*Reference*
Ammonium Thioglycolate	Mice (20–25 g), no. not stated	i.p. injection	LD_{50} = 100–200 mg/kg	62
Ammonium Thioglycolate (53.6%)	22 Sherman rats	i.p. injection	LD_{50} = 165 ± 7 mg/kg	63
Ammonium Thioglycolate (10.7%)	27 mice	i.p. injection	LD_{50} = 200 ± 13 mg/kg	63
Thioglycolic Acid	ddy mice, no. not stated	i.p. injection	LD_{50} = 368–737 mg/kg	64
Sodium Thioglycolate	CF_1 mice, no. not stated	i.p. injection	LD_{50} = 200–300 mg/kg	62
Sodium Thioglycolate (5%)	10 Osborne-Mendel rats (140–200 g)	i.p. injection	LD_{50} = 126 ± 9 mg/kg	46
Sodium Thioglycolate (5%)	10 CAF_1 mice (15–24 g)	i.p. injection	LD_{50} = 505 ± 57 mg/kg	46
Ammonium Thioglycolate (53.6%)	12 rabbits	i.v. injection	LD_{50} = 100 mg/kg	63
Ammonium Thioglycolate (53.6%)	5 cats	i.v. injection	LD_{50} = 175 mg/kg	63
Thioglycolic Acid (5%)	Dogs, no. not stated	i.v. injection; doses = 105, 300, 500, and 600 mg/kg	500 and 600 mg/kg doses caused death	46
Thioglycolic Acid (5%)	1 monkey	i.v. injection; dose = 300 mg/kg	Death at 10 h postinjection	46

Subchronic Intraperitoneal Toxicity

Sodium Thioglycolate

Sodium Thioglycolate, 100 mg/kg of 5% solution, was administered to five fasted male rats (125 ± 32.1 g) of the Osborne-Mendel (Yale) strain via intraperitoneal injection. The untreated control group consisted of five rats of the same strain. Injections were made 5 days per week during a 24-week period. Two of the treated animals died accidentally before the sixteenth week. At the end of the 24-week period, there was no significant difference in weight gain between treated and control groups. At necropsy, no significant gross lesions were observed. The following organs were examined microscopically: liver, kidneys, adrenal glands, spleen, thyroid gland, and pancreas. The only tissue alteration attributable to Sodium Thioglycolate administration was minimal to slight hyperplasia of the thyroid gland.[46]

Acute Dermal Toxicity

Ammonium Thioglycolate

The dermal toxicity of a permanent waving solution (pH 7.0) containing 10.98% Ammonium Thioglycolate and 1.0% diammonium dithioglycolate was evaluated using 24 New Zealand albino rabbits (12 males, 12 females; 2.3–3.0 kg). The solution was

held in contact with the skin (clipped free of hair) of the trunk for 24 h by means of an impervious sleeve. The skin of 12 animals was abraded before application. Slight erythema was noted at the application site of each animal tested. The mean LD_{50} (24 animals) was 7.9 ± 0.5 ml/kg.[65]

Glyceryl Thioglycolate

The dermal toxicity of 100 ml of a commercial acid wave (pH 6.9–7.2) containing 22% Glyceryl Thioglycolate was evaluated using eight New Zealand albino rabbits (weight 2.44–3.16 kg). The product (22.3 ml) was applied to dorsal skin, clipped free of hair, in doses of 4556 mg/kg (4 rabbits) and 3038 mg/kg (4 rabbits). Each application site was approximately 30% of the total body surface area. The area of the application site was not stated. The skins of two animals in both dose groups were abraded before application. Abraded and intact sites were covered by wrapping the trunk of each animal with an impervious plastic sleeve that was taped securely in place. The product was rinsed from the skin 24 h after application, and animals were observed for 14 days. Two of the rabbits receiving the 4556 mg/kg dose died, and one rabbit died in the group receiving the 3038 mg/kg dose. The product was classified as practically nontoxic, and the LD_{50} was between 3038 mg/kg and 4556 mg/kg.[66]

Short-Term Dermal Toxicity

Ammonium Thioglycolate

The dermal toxicity of a cold wave product (pH 7.3–7.6) containing 17.5% Ammonium Thioglycolate was evaluated in a 21-day study using three groups of 12 New Zealand White rabbits (18 males, 18 females; weights 1.5–3.5 kg). The three groups were given doses of 0.25, 0.5, and 0.75 ml/kg, respectively, on days 1 and 2. On days 3 to 5, the product was diluted with an equal volume of water and administered to the three groups at doses of 0.5, 1.0, and 2.0 ml/kg, respectively. A group of 12 animals dosed with distilled water (0.75 ml/kg) served as the control. Doses were applied to dorsal skin (clipped free of hair) via a syringe. Sites on three animals per group were abraded. Each site was covered with a patch made of gauze (1–2 layers) and an occlusive binder for 4 h. Sites were then wiped clean, and irritation reactions were scored according to the Draize scale.[67] Severe erythema was observed in 29 animals (8 low-dose, 11 mid-dose, and 10 high-dose) by day 3 of the study. Dilution of the product did not reduce significantly the extent of dermal irritation, so the study was ended after the first week. Only one death (day 3, high-dose group) was reported. Nine animals were necropsied: controls (2 animals), low and mid-dose groups (2 animals/group), and high-dose group (3 animals). Eschar was observed at test sites of six of the seven experimental animals, including the animal that died. Gross findings indicative of gastroenteritis were also noted in this animal. Lesions were not observed in control animals. The cause of death was not related to test substance administration.[68]

The dermal toxicity of 16 lotions containing 0.6 N Ammonium Thioglycolate and one lotion containing 0.6 N Sodium Thioglycolate was evaluated using groups of male and female rabbits (weights 2.3–3.0 kg, strain not stated). All but one of the lotions contained a commercial wetting agent. Each lotion was applied to shaved skin (right side) daily for 20 consecutive days. The last application was followed by a 3-week observation period, after which LD_{50}'s were calculated. The LD_{50} (mg of Thioglycolic Acid/kg/day) was defined as the daily dosage causing death in 50% of the animals

treated for 20 days and observed for 3 weeks. At the conclusion of testing, tissues from the animals were examined grossly and microscopically. The highest toxicity (LD_{50} = 50.0 ± 3.6 mg/kg, 33 animals) was noted in the group treated with the lotion containing Ammonium Thioglycolate and 10% active benzalkonium chloride. The least toxicity (LD_{50} > 365 mg/kg, 12 animals) was noted in the group treated with the lotion containing Ammonium Thioglycolate and no wetting agent. An LD_{50} of 93.3 ± 6.1 mg/kg was reported for the group (35 rabbits) treated with the lotion containing Sodium Thioglycolate and 4% active Triton X-200. The only extreme cutaneous alterations reported were those observed after administration of the lotion that contained Ammonium Thioglycolate and 0.5% active benzalkonium chloride. In this group, intense inflammation was noted as early as after the first or second application. Widespread irritation and necrosis were observed later. Weight losses were excessive. The alteration observed during gross and microscopic examinations (all treatment groups) was pulmonary congestion in a few rabbits.[49]

Glyceryl Thioglycolate

The dermal toxicity of an acid wave product (pH 6.9–7.2) containing 22.6% Glyceryl Thioglycolate was evaluated in a 28-day study using New Zealand rabbits (5 males, 5 females). The animals were approximately 10 to 13 weeks old and weighed 2.38 to 2.84 kg. The product was applied (dose = 2.0 ml/kg, 30 min exposure) via a syringe to dorsal skin clipped free of hair. Sites were rinsed and dried after exposure. This procedure was repeated 5 days per week for 4 weeks (20 applications). Ten untreated rabbits served as controls. The only death reported was one rabbit from the untreated control group. Severe to complete hair loss at application sites was observed in all experimental animals after repeated exposures. Fissures were noted at the application sites of three animals. Results from microscopic examination of sections of skin and hematological studies indicated no treatment-related effects.[69]

Subchronic Dermal Toxicity

Ammonium Thioglycolate

The dermal toxicity of cold wave solutions (pH 9.0–9.5) containing 7.0% Ammonium Thioglycolate was evaluated using albino rabbits. Four cold wave solutions were applied to the skin via inunction at doses of 0.5, 1.0, 2.0, and 4.0 ml/kg, respectively, for 90 days. Eleven of 18 rabbits given 4.0 ml/kg doses and 2 of 17 rabbits given 2.0 ml/kg doses died. No deaths occurred in groups dosed with 1.0 ml/kg (17 rabbits) and 0.5 ml/kg (15 rabbits). The lesion observed at microscopic examination of sections of skin from approximately 50 animals was a mild dermatitis.[70]

Ocular Irritation

Ammonium Thioglycolate

The ocular irritation potential of a cold wave product (pH 7.3–7.6) containing 17.5% Ammonium Thioglycolate was evaluated using nine New Zealand white rabbits. The product (0.1 ml) was instilled into one conjunctival sac of each animal. The eyes of three animals were rinsed after instillation. Untreated eyes served as controls. Ocular reactions were scored at 1, 2, 3, 4, and 7 days postinstillation according to the

Draize scale. On day 1, conjunctival redness was observed in the unrinsed eyes of three of the six rabbits. Reactions had cleared by day 3. One of the three rabbits (rinsed eyes) also had conjunctival redness on day 1. The reaction had cleared by day 3. The Draize scores at 24 h postinstillation were 1.0 and 0.7 for unrinsed and rinsed eyes, respectively (Table 5).[71] Additional ocular irritation studies of formulations containing Ammonium Thioglycolate (5–10.98%) are summarized in Table 5.

Glyceryl Thioglycolate

The ocular irritation potential of a commercial acid wave (pH 6.9–7.2) containing 22% Glyceryl Thioglycolate was evaluated using 9 New Zealand albino rabbits. The product was instilled into the conjunctival sac of the right eye. The eyes of 3 rabbits were rinsed. Untreated eyes served as controls. Reactions were scored at 1 h and 1, 2, 3, and 7 days postinstillation according to the Draize scale: 0 to 110. Draize scores for rinsed and unrinsed eyes were 9 and 6, respectively. The product was minimally irritating to the eyes (rinsed and unrinsed) of rabbits (Table 5).[72] Ocular irritation studies of other formulations containing Glyceryl Thioglycolate are summarized in Table 5.

Skin Irritation

Ammonium Thioglycolate

Hydrophilic ointments containing various concentrations of Ammonium Thioglycolate (0.05–30%) were applied to the skins of 10 Hartley guinea pigs. Skin irritation was not noted (Table 6).[73]

The skin irritation potential of a cold wave product (pH 7.3–7.6) containing 17.5% Ammonium Thioglycolate was evaluated using four New Zealand white rabbits. The product was applied via an occlusive patch for 4 h to abraded and intact skin. Reactions were scored at 4, 24, and 72 h postapplication according to the scales: 1 (very slight erythema) to 4 (severe erythema to slight eschar formation); 1 (very slight edema) to 4 (severe edema). Well-defined erythema and slight edema accounted for the majority of reactions (abraded and intact sites) observed at 4 and 24 h. Reactions observed at 72 h were very slight erythema and edema. The product had the potential for inducing moderate skin irritation, and the primary irritation index was 2.30 (Table 6).[86] In a second study, the skin irritation potential of the same cold wave product was evaluated using a procedure in which patches were applied to abraded and intact skin for 24 h. The primary irritation index was 2.45, and the product had the potential for inducing moderate skin irritation (Table 6).[86]

The skin irritation potential of a permanent waving solution containing 7.1% Ammonium Thioglycolate and 1.2% ammonium hydroxide was evaluated using six albino rabbits. The solution was applied to the trunk (shaved and abraded skin), and sites were covered with gauze patches for 24 h. Reactions were scored at 24 and 72 h postapplication according to the scales: 0 (no erythema) to 4 (severe erythema to slight eschar formation); 0 (no edema) to 4 (severe edema). The irritation index was 0.1, classifying the solution as a nonirritant (Table 6).[90] The solution was also classified as a nonirritant (irritation index = 0.6) in an earlier study (same procedure).[91] Additional skin irritation studies on Ammonium Thioglycolate and hair waving formulations containing Ammonium Thioglycolate are summarized in Table 6.

TABLE 5. OCULAR IRRITATION

Test substance	No. of animals	Procedure	Results	Reference
Cold wave (17.5% Ammonium Thioglycolate)	9 New Zealand rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 7 postinstillation	Transient ocular reactions	71
Permanent waving solution (10.98% Ammonium Thioglycolate)	9 albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 postinstillation	Nonirritant	74
Permanent waving solution (8.3% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 7 postinstillation	Moderate ocular irritant	75
Permanent waving solution (7.2% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 7 postinstillation	Moderate ocular irritant	76
Permanent waving solution (7.1% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 7 postinstillation	Nonirritant	77
Permanent waving lotion (7.0% Ammonium Thioglycolate)	9 New Zealand white rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 postinstillation	Borderline ocular irritant (unrinsed eyes) Nonirritant (rinsed eyes)	78
Permanent waving lotion (7.0% Ammonium Thioglycolate)	9 rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 postinstillation	Minimal irritant (unrinsed eyes). Nonirritant (rinsed eyes)	79
Permanent waving lotion (7.0% Ammonium Thioglycolate)	9 rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 postinstillation	Nonirritant	79
Permanent waving lotion (7.0% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 postinstillation	Ocular irritant	80
Permanent waving lotion (5.8% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 postinstillation	Moderate ocular irritant	81
Permanent waving solution (5.0% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 postinstillation	Nonirritant	82
Acid wave (22% Glyceryl Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 7 postinstillation	Minimal ocular irritant	72
Exothermic acid wave (21% Glyceryl Thioglycolate)	3 New Zealand rabbits	Reactions scored up to day 7 postinstillation	Nonirritant	83
Waving lotion (conc. of Glyceryl Thioglycolate not stated)	9 albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 14 postinstillation	Nonirritant (rinsed eyes). Slight irritant (unrinsed eyes)	84
Waving lotion (conc. of Glyceryl Thioglycolate not stated)	9 albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 14 postinstillation	Nonirritant	85

TABLE 6. SKIN IRRITATION

Test substance	No. of animals	Procedure	Results	Reference
Hydrophilic ointments (0.05–30% Ammonium Thioglycolate)	10 Hartley guinea pigs	Not stated	Nonirritant	73
Cold wave (17.5% Ammonium Thioglycolate)	4 New Zealand white rabbits	4 h application to abraded and intact skin (occlusive patches)	Moderate skin irritant	86
Cold wave (17.5% Ammonium Thioglycolate)	4 New Zealand white rabbits	24 h application to abraded and intact skin (semiocclusive patches)	Moderate skin irritant	86
Permanent waving lotion (10.98% Ammonium Thioglycolate)	6 rabbits (strain not stated)	24 h application to abraded and intact skin	Nonirritant	87
Permanent waving lotion (8.3% Ammonium Thioglycolate)	6 New Zealand rabbits	24 h application to abraded skin (gauze patches)	Moderate irritant	88
Permanent waving solution (7.2% Ammonium Thioglycolate)	6 New Zealand rabbits	24 h application to abraded skin (gauze patches)	Primary dermal irritant	89
Permanent waving solution (7.1% Ammonium Thioglycolate)	6 albino rabbits	24 h application to abraded and intact skin (gauze patches)	Nonirritant	90
Permanent waving solution (7.0% Ammonium Thioglycolate)	6 albino rabbits	24 h application to abraded and intact skin (gauze patches)	Corrosive material	92
Permanent waving solution (7.0% Ammonium Thioglycolate)	6 rabbits (strain not stated)	24 h application to abraded and intact skin	Nonirritant	93
Permanent waving solution (7.0% Ammonium Thioglycolate)	6 New Zealand rabbits	24 h application to abraded and intact skin	Slight irritant	94
Ammonium Thioglycolate (4–7% solutions)	Rabbits (no. and strain not stated)	1 h application	Nonirritant	95
Ammonium Thioglycolate (7.0%)	Rabbits (no. and strain not stated)	24 h application to abraded and intact skin (cotton patches)	Skin irritant	95
Ammonium Thioglycolate (6.5%)	Rabbits (no. and strain not stated)	24 h application to abraded and intact skin (cotton patches)	Skin irritant (abraded skin). Nonirritant (intact skin)	95
Permanent waving solution (5.8% Ammonium Thioglycolate)	6 New Zealand rabbits	24 h application to abraded and intact skin (gauze patches)	Severe irritant	96
Permanent waving solution (5.0% Ammonium Thioglycolate)	6 New Zealand rabbits	24 h application to abraded and intact skin (gauze patches)	Minimal irritant	97
Glyceryl Thioglycolate (100%)	6 New Zealand white rabbits	24 h application to abraded and intact skin (occlusive patches)	Severe irritant	98
Acid wave (22% Glyceryl Thioglycolate)	6 New Zealand albino rabbits	24 h application to abraded and intact skin (occlusive patches)	Mild irritant	99
Exothermic acid wave (21% Glyceryl Thioglycolate)	6 New Zealand white rabbits	24 h application to abraded and intact skin (occlusive wrapping)	Severe irritant	100
Commercial wave product (10.0–22% Glyceryl Thioglycolate)	6 New Zealand white rabbits	2 h application to abraded and intact skin (occlusive patches)	Mild irritant	101

Glyceryl Thioglycolate

The skin irritation potential of undiluted Glyceryl Thioglycolate was evaluated using six New Zealand white rabbits (weights 2–4 kg). The test substance was applied (0.5 ml, occlusive patches) for 24 h to abraded and intact skin, clipped free of hair, of the back and flanks. Patches were covered with an occlusive binder, consisting of a layer of plastic wrap, a protective cloth, and a stockingnette sleeve, that was taped to the skin. Reactions were scored 24 and 72 h after patch application. Erythema and eschar formation were scored according to the scale: 0 (none) to 4 (severe erythema to slight eschar formation). Edema was scored according to the scale: 0 (none) to 4 (severe). Severe erythema to slight eschar formation was observed in all animals (abraded and intact skin) at 24 and 72 h postapplication. Severe and moderate edema (abraded and intact skin) was observed in all animals at 24 and 72 h postapplication, respectively. It was concluded that Glyceryl Thioglycolate was extremely irritating to the skin of rabbits (Table 6).[98]

The skin irritation potential of a commercial acid wave (pH 6.9–7.2) containing 22% Glyceryl Thioglycolate was evaluated using six New Zealand albino rabbits. The product was applied to two sites (one intact, one abraded) located lateral to the midline of the back. Each site had been clipped free of hair. After application of the product, each site was covered with an occlusive patch that was secured with masking tape. The trunk of each animal was also wrapped with an impervious plastic sleeve. The product was rinsed from the skin after 24 h of exposure. Reactions (erythema and edema) were scored immediately after patch removal and 2 days later, according to the scale: 0 to 4. The primary irritation score was 2.2 (max = 8), indicating that the product was mildly irritating to the skin of rabbits (Table 6).[99] Additional skin irritation studies of hair waving formulations containing Glyceryl Thioglycolate are summarized in Table 6.

Skin Irritation and Sensitization

Thioglycolic Acid

The skin irritation and sensitization potentials of 9.0% Thioglycolic Acid (pH 8) were evaluated using the open epicutaneous test. Eight guinea pigs were tested. The test substance (0.1 ml) was applied to an 8 cm^2 area of skin (clipped free of hair) on the flank daily for 21 days (induction phase). Sites were graded at the end of each 24 h period, weekends excluded, according to the scale: 0 (no skin irritation) to 4 (severe skin irritation). On days 21 and 35 (challenge phase), the test substance was applied to the contralateral flank. Sites were graded 24 and 48 h after application. During the induction phase, reactions ranging from slight skin irritation to well-defined skin irritation were observed in 7 animals. Reactions ranging from slight skin irritation to moderate skin irritation were observed in 1 animal. Reactions were not observed during the challenge phase. The test substance was an irritant, but not a sensitizer.[102]

Glyceryl Thioglycolate

The skin irritation and sensitization potentials of 22% Glyceryl Thioglycolate (pH 7.4) were evaluated using the open epicutaneous test. Eight guinea pigs were tested. The test substance (0.1 ml) was applied to an 8 cm^2 area of skin (clipped free of hair) on the flank daily for 21 days (induction phase). Sites were graded at the end of each 24 h period, weekends excluded, according to the scale: 0 (no skin irritation) to 4 (severe skin irritation). On days 21 and 35 (challenge phase), the test substance was applied to

the contralateral flank. Sites were graded 24 and 48 h after application. During the induction phase, reactions ranging from slight skin irritation to moderate skin irritation were observed in all animals. Reactions were not observed during the challenge phase.[103]

A skin irritation and sensitization study of 80.31% Glyceryl Thioglycolate (22% v/v in water, pH 7.4) was conducted with 8 white spotted, Himalayan guinea pigs (weights 300–450 g). The effective concentration of Glyceryl Thioglycolate in the test solution was approximately 18%. The test substance (0.1 ml) was applied to an 8 cm^2 area on the flank (clipped free of hair) 5 days per week for 3 weeks. Sites were not covered. Reactions were graded 24 h after each application. On days 21 and 35 (challenge phase), the test substance was applied to the contralateral flank. Sites were graded 24 and 48 h after application. Eight control animals were not treated during the induction phase but were treated with the test substance during the challenge phase (same procedure). During the induction phase, moderate erythema predominated in experimental animals. No sensitization reactions were observed during the challenge phase. Reactions were not observed in control animals.[104]

Skin Sensitization

Ammonium Thioglycolate

The sensitization potential of Ammonium Thioglycolate was evaluated using the closed epicutaneous test. During the induction phase, 30% Ammonium Thioglycolate was applied to the skins of 8 guinea pigs (Hartley strain). The animals were challenged with concentrations of Ammonium Thioglycolate ranging from 0.2% to 30.0%. Four animals had sensitization reactions to 30.0% Ammonium Thioglycolate, whereas none had reactions to 0.2% Ammonium Thioglycolate. It was concluded that Ammonium Thioglycolate was a mild sensitizer (Table 7).[73]

In another study, the sensitization potential of Ammonium Thioglycolate was evaluated using the epicutaneous test. Ammonium Thioglycolate was dissolved in a mixture consisting of methyl cellosolve and Tween 80 and applied at concentrations of 1, 2, 5, and 10% to the flanks of 20 white guinea pigs (inbred strain). Initially, the animals were sensitized by applying 10% Ammonium Thioglycolate to the flanks daily for 10 days. The animals were later challenged with 1, 2, and 5% Ammonium Thioglycolate. Weak sensitization reactions to 5.0% Ammonium Thioglycolate were observed in three guinea pigs. None of the guinea pigs had sensitization reactions to 2% or 1% Ammonium Thioglycolate. In a second experiment, 40 guinea pigs were sensitized to derivatives of Thioglycolic Acid (same procedure) and later challenged with 5% Ammonium Thioglycolate. Half of the animals were sensitized to 10% Thioglycolic Acid hydrazide, and the remaining half were sensitized to 10% Thioglycolic Acid glycolester. Weak sensitization reactions to 5% Ammonium Thioglycolate were observed only in two animals that had been sensitized to Thioglycolic Acid hydrazide.[105]

The sensitization potential of a permanent waving solution containing 7.0% Ammonium Thioglycolate, 5.0% urea, and 1.2% ammonium hydroxide was evaluated using the maximization test. During the first phase of induction, 10 Hartley guinea pigs were given intradermal injections of the waving solution (concentration 5%). The effective concentration of Ammonium Thioglycolate in these injections was 0.35%. The solution was injected alone and in Freund's complete adjuvant. After a 7-day

TABLE 7. SKIN SENSITIZATION

Test substance	*Concentration tested*	*No. of animals*	*Procedure*	*Results*	*Reference*
Ammonium Thioglycolate	30% (induction). 0.2%–30% (challenge)	8 guinea pigs	Closed epicutaneous test	Mild sensitization	73
Ammonium Thioglycolate	10% (induction). 1%–5% (challenge)	20 white guinea pigs	Epicutaneous test	Weak sensitization	105
7% Ammonium Thioglycolate (in permanent waving solution)	0.35% Ammonium Thioglycolate (induction). 7% Ammonium Thioglycolate (challenge)	10 Hartley guinea pigs	Maximization test	No sensitization	106
8.3% Ammonium Thioglycolate (in permanent waving solution)	8.3% Ammonium Thioglycolate (induction). 6.2% and 1.2% Ammonium Thioglycolate (challenge)	10 Hartley guinea pigs	Maximization test	No sensitization	108
7.2% Ammonium Thioglycolate (in permanent waving solution)	7.2% Ammonium Thioglycolate (induction). 5.4% and 1.1% Ammonium Thioglycolate (challenge)	10 Hartley guinea pigs	Maximization test	No sensitization	109
5.8% Ammonium Thioglycolate (in permanent waving solution)	0.29% and 4.4% Ammonium Thioglycolate (induction). 4.4% and 0.88% Ammonium Thioglycolate (challenge)	10 Hartley guinea pigs	Maximization test	No allergic reactions	110

7.0% Ammonium Thioglycolate (in permanent waving solution)	7.0% and 0.35% Ammonium Thioglycolate (induction). 3.5% Ammonium Thioglycolate (challenge)	10 Hartley guinea pigs	Maximization test	No allergic reactions	111
1.14% Ammonium Thioglycolate (in permanent waving solution)	As is (1st induction and challenge). 0.057% Ammonium Thioglycolate (2nd induction)	10 Hartley guinea pigs	Maximization test	No sensitization	112
10.98% Ammonium Thioglycolate (in permanent waving solution)	0.5% Ammonium Thioglycolate (induction and challenge)	10 Hartley albino guinea pigs	Maximization test	No sensitizaiton	113
Thioglycolic Acid (1.25% aqueous)	1.25% Thioglycolic Acid (induction). 2.5% Thioglycolic Acid (challenge)	10 Hartley or Connaught guinea pigs	Ten intradermal injections (induction). Animals challenged 10–14 days after induction period	No sensitization	114
Glyceryl Thioglycolate (80%)	As is	10 Hartley guinea pigs	Three 6 h exposures (induction); 24 h challenge after 2 weeks nontreatment period	No sensitization	115
Glyceryl Thioglycolate (80%)	48%	6 guinea pigs	Open epicutaneous test	No sensitization	117
Glyceryl Thioglycolate (80%)	24%	8 guinea pigs	Open epicutaneous text	No sensitization	117

nontreatment period, the waving solution (full strength) was applied topically for 48 h (second induction). The animals were challenged with a 24-h topical application of the solution (full strength) 2 weeks later. Sensitization reactions were scored according to the scale: 0 (no reaction) to 3 (intense redness and swelling). Sensitization reactions were not observed in any of the animals tested (Table 7).[106]

The maximization test[107] was also used to evaluate the skin sensitization potential of a permanent waving solution containing 8.3% Ammonium Thioglycolate and 1.40% ammonium hydroxide. The solution was tested at concentrations of 15% and 75%, effective Ammonium Thioglycolate concentrations of 1.2% and 6.2%, respectively. Sensitization reactions were not observed in any of the 10 Hartley guinea pigs tested (Table 7).[108] The sensitization potential of another permanent waving solution containing 7.2% Ammonium Thioglycolate and 1.5% ammonium hydroxide also was evaluated (same procedure) using 10 Hartley guinea pigs. The solution was tested at concentrations of 15% and 75%, effective Ammonium Thioglycolate concentrations of 1.1% and 5.4%, respectively. The solution was not a sensitizer (Table 7).[109]

The maximization test[107] was used to evaluate the sensitization potential of a permanent waving solution containing 5.8% Ammonium Thioglycolate and 1.28% ammonium hydroxide. Ten Hartley guinea pigs (weights 300–500 g) were tested. During the first induction, 5.0% solutions of the test substance (effective concentration of Ammonium Thioglycolate 0.29%) in deionized water and Freund's complete adjuvant were injected intradermally. During the second induction, a 75.0% solution of the test substance (effective concentration of Ammonium Thioglycolate 4.4%) was applied via a topical induction patch. The animals were challenged with test solutions containing 4.4% and 0.88% Ammonium Thioglycolate. Sites were scored 24 and 48 h after challenge patch application according to the scale: 0 (no reaction) to 3 (intense redness and swelling). Allergic reactions were not observed in any of the animals tested (Table 7).[110] Similar results were observed with Hartley guinea pigs when a permanent waving solution containing 7.0% Ammonium Thioglycolate and 1.2% ammonium hydroxide was tested (same procedure) at a concentration of 50% (effective concentration of Ammonium Thioglycolate 3.5%) during the challenge phase (Table 7).[111]

The sensitization potential of a permanent waving solution containing 1.14% Ammonium Thioglycolate and 1.17% ammonium hydroxide was evaluated using the maximization test and 10 Hartley albino guinea pigs.[107] During the first induction, the solution, both undiluted and emulsified in Freund's adjuvant, was injected intradermally. The solution was applied at a concentration of 5.0% (effective concentration of Ammonium Thioglycolate 0.057%) via a topical induction patch during the second induction. The animals were patch tested with undiluted solution during the challenge phase. Allergic reactions were not observed in any of the animals tested (Table 7).[112]

The sensitization potential of another permanent waving solution (pH 7) containing 10.98% Ammonium Thioglycolate and 1.0% diammonium dithioglycolate was evaluated according to the modified Kligman-Magnusson maximization test. The product was diluted with distilled water and Freund's adjuvant to a concentration of 5.0% (effective concentration of Ammonium Thioglycolate 0.5%) and administered to 10 Hartley albino guinea pigs (weights 300–500 g). Initially, the diluted product was injected intradermally into the anterior dorsal region (clipped free of hair) of each animal. At 7 days postinjection, the test substance was applied for 48 h to shaved skin (same sites) via occlusive patches secured with adhesive tape. After a 14-day nontreatment period, an occlusive patch moistened with the test substance was applied for 24 h to the flank (clipped free of hair) of each animal. Sites were scored 24 and 48 h after

patch removal according to the scale: 0 (no reactions) to 3 (intense redness and swelling). Positive controls (2 animals) and negative controls (2 animals) were treated with 5% formalin and water, respectively, according to the aforementioned procedure. The test substance did not induce sensitization reactions in any of the animals tested (Table 7).[113]

The sensitization potential of an aqueous solution of 1.25% Thioglycolic Acid (adjusted to pH 9.0–9.3 with ammonia) was evaluated using 10 Hartley or Connaught guinea pigs (weight 300 g). The solution was injected intradermally (shaved skin on one side) into each animal three times per week for a total of 10 injections. The first dose injected was 0.05 ml, and subsequent doses were each 0.10 ml. Between 10 and 14 days after the tenth injection, the animals were challenged (new test sites) with 0.05 ml of 2.5% Thioglycolic Acid. Four or five guinea pigs served as untreated controls. Sensitization reactions were not observed in any of the animals (Table 7).[114]

Glyceryl Thioglycolate

The sensitization potential of 80.0% Glyceryl Thioglycolate was evaluated using 10 male Hartley guinea pigs (380–423 g). The test substance (0.5 ml) was applied to the shoulder-flank (clipped free of hair) via a Webril patch. Each patch was covered with plastic. The patch and plastic covering were held in place with tape for 6 h. This procedure was repeated (same site) once per week for 3 weeks. After a 2-week nontreatment period, challenge patches were applied according to the aforementioned procedure. Patches remained in place for 24 h, and sites were scored 24, 48, and 72 h after patch application according to the scale: 1 (slight erythema) to 3 (marked erythema). Positive controls (10 guinea pigs) and negative controls (10 guinea pigs) received applications of 0.1% dinitrochlorobenzene and distilled water, respectively, according to the same procedure. Glyceryl Thioglycolate did not induce sensitization reactions in any of the animals tested (Table 7).[115]

The sensitization potential of commercial 80% Glyceryl Thioglycolate (pH 2.3–3.3) was evaluated using the open epicutaneous test.[116] Six guinea pigs were tested with a 60% concentration of the test substance (effective concentration of Glyceryl Thioglycolate 48%). Eight guinea pigs were tested with a 30% concentration of the test substance (effective concentration of Glyceryl Thioglycolate 24%). No evidence of contact sensitization was observed in either of the two groups tested (Table 7).[117]

MUTAGENICITY

Ammonium Thioglycolate

The mutagenicity of Ammonium Thioglycolate was evaluated according to the procedure of Ames et al.[118] using strains 1535, 1537, and 1538 of *Salmonella typhimurium*. The concentrations tested ranged from 0.25 to 5.0 mg/plate in strain 1535 and 1538 cultures and from 0.5 to 5.0 mg/plate in strain 1537 cultures. Ammonium Thioglycolate was not mutagenic (Table 8).[119]

Thioglycolic Acid

The mutagenicity of Thioglycolic Acid was evaluated according to the procedure by Ames et al.[118] using strains TA 1535, TA 1537, and TA 1438 of *S. typhimurium* LT2.

TABLE 8. MUTAGENICITY

Test substance	*Concentration tested*	*Strains tested*	*Procedure*	*Results*	*Reference*
Ammonium Thioglycolate	0.25–5.0 mg/plate	*Salmonella typhimurium* strains 1535, 1537, and 1538	Ames et al.[118] Presence and absence of metabolic activation	Not mutagenic	119
Thioglycolic Acid (in DMSO)	1 to 1000 μg/plate	*S. typhimurium* strains TA 1535, TA 1537, and TA 1538	Ames et al.[118] Presence and absence of metabolic activation	Not mutagenic	120
Thioglycolic Acid	Not stated	*Escherichia coli* strain Sd-4-73	Paper disk method by Iyer and Szybalski[121]	Not mutagenic	122
Thioglycolic Acid (in sucrose solution)	0.5%	Flies of the Canton-S strain	Sex-linked recessive lethal mutations test	Not mutagenic	123
Glyceryl Thioglycolate	0.25–5.0 mg/plate	*S. typhimurium* strains 1535, 1537, and 1538	Ames et al.[118] Presence and absence of metabolic activation	Not mutagenic	119
Glyceryl Thioglycolate (1% in DMSO)	0.02–1.50 mg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1537, and TA 1538	Presence and absence of metabolic activation. (procedure not stated)	Not mutagenic	104
Sodium Thioglycolate	Up to 3600 μg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, and 1537, and TA 1538	Ames et al.[118] Presence and absence of metabolic activation	Not mutagenic	125
Sodium Thioglycolate (in 5% saccharose)	25 mM	Berlin K and Basc strains of *Drosophila melanogaster*	Sex-linked recessive lethal mutations test	Not mutagenic	125
Sodium Thioglycolate	As is	3 mice (strain not stated)	Micronucleus test	Not mutagenic	125

Thioglycolic Acid (diluted with DMSO) was tested at concentrations of 1, 10, 100, and 1000 μg/plate with and without metabolic activation. All concentrations were incubated with each bacterial strain for 48 h (37°C), after which the number of revertant colonies was determined. DMSO was the negative control. β-naphthylamine, neutral red, and 2-acetylaminofluorene served as positive controls. Thioglycolic Acid was not mutagenic with and without metabolic activation (Table 8).[120]

In another study, the mutagenicity of Thioglycolic Acid was evaluated in strain Sd-4-73 of *Escherichia coli* via the paper disk method.[121] Bacteria were inoculated into a medium consisting of nutrient broth and streptomycin (20 μg/ml). A microdrop solution (0.01–0.025 ml) or a crystal of the test substance was applied to a filter paper disk positioned on each agar plate. Mutagenicity was indicated by an increase in the frequency of reversion from streptomycin dependence to independence. Thioglycolic Acid was not mutagenic (Table 8).[122]

The sex-linked recessive lethal mutations test was used to evaluate the mutagenic potential of Thioglycolic Acid. A 0.5% solution of the test substance was formed by dissolving Thioglycolic Acid (0.5 ml) in 100 ml of control solution. The control solution was a 1% sucrose solution containing 1 M KOH and carmine (red dye). Male flies (4–5 days old) of the Canton-S strain were fed (24 h) from a pad immersed with the test solution. Only insects with abdomens coated with the red dye were used in the mutagenicity test. The test solution was not mutagenic to any of the 309 X chromosomes tested (Table 8).[123]

Glyceryl Thioglycolate

The mutagenicity of Glyceryl Thioglycolate was evaluated according to the procedure of Ames et al.[118] using strains 1535, 1537, and 1538 of *S. typhimurium*. The concentrations tested ranged from 0.25 to 5.0 mg/plate. Glyceryl Thioglycolate was not mutagenic (Table 8).[119]

The mutagenicity of 1% Glyceryl Thioglycolate (in DMSO) was evaluated (procedure not stated) using strains TA 1538, TA 98, TA 100, and TA 1537 of *S. typhimurium*. The concentrations tested ranged from 0.02 to 1.50 mg/plate with and without metabolic activation. The test substance was not mutagenic (Table 8).[124]

Sodium Thioglycolate

The mutagenic potential of Sodium Thioglycolate was evaluated using the *Salmonella*/mammalian-microsome mutagenicity test.[118] Strains TA 1535, TA 100, TA 1538, TA 98, and TA 1537 of *S. typhimurium* were each tested with at least five doses of Sodium Thioglycolate with and without metabolic activation. The maximum concentration tested was 3600 μg/plate. The test substance did not induce mutagenic effects in any of the strains tested (Table 8).[125]

In another study, the mutagenic potential of Sodium Thioglycolate was evaluated using the sex-linked recessive lethal mutations test.[126] One dose (close to the LD_{50}) of 25 mM Sodium Thioglycolate in 5.0% saccharose was fed to Berlin K (wild type) and Basc strains of *Drosophila melanogaster*. Approximately 1200 X chromosomes were tested per experiment in each of three successive broods. In repeat experiments, sometimes only single broods were tested. F_2 progeny cultures with two or fewer

wild-type males were routinely retested in the F_3 generation to confirm X-linked recessive lethal mutations. The test substance was not mutagenic (Table 8).[125]

The mutagenic potential of Sodium Thioglycolate also was evaluated using the micronucleus test.[127] Two doses of the test substance (285 mg/kg each) were administered intraperitoneally to 3 mice at 0 and 24 h. One animal served as the control. Bone marrow smears were prepared 30 h after administration of the first dose. One thousand polychromatic erythrocytes per mouse were scored. The test substance was not mutagenic (Table 8).[125]

CARCINOGENICITY

Sodium Thioglycolate

The carcinogenicity of Sodium Thioglycolate was evaluated using 94 Swiss female mice (7 weeks old) from the Eppley colony and 10 female rabbits (8 weeks old). A 1.0% solution (0.02 ml) of the test substance in acetone was applied twice per week to the shaved skin (interscapular region) of each of 49 mice and to the inside of the left ear of each of 5 rabbits. Sodium Thioglycolate was also similarly applied at a concentration of 2% in acetone to 45 mice and 5 rabbits. Ninety-three mice and 5 rabbits served as negative controls. Positive control groups, 40 mice and 5 rabbits, were treated with 7,12-dimethylbenz[a]anthracene. All mice were allowed to die, whereas the rabbits were killed at week 85. None of the experimental or control mice survived beyond week 120 of treatment. Infectious diseases, such as pneumonia and hepatitis, occurred in a small number of animals, resulting in an increased number of deaths. Large numbers of neoplasms were observed in treated and negative control mice: lymphomas, pulmonary adenomas, hepatic hemangiomas, ovarian neoplasms, and dermal fibromas. Epidermal neoplasms were not observed. Differences in the incidence of neoplasms between experimental and negative control mice were not significant. No neoplasms were observed in rabbits. No significant decrease in the life span of mice or rabbits in experimental groups was observed. Sodium Thioglycolate was not carcinogenic.[128]

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation

Primary skin irritation usually is noted when Thioglycolates, high pH solutions, are tested using "covered" patches. In the patch test procedure, Thioglycolates remain in contact with the skin for at least 24 h, making a primary irritant reaction likely. However, under conditions of actual usage, cold wave solutions are not in intimate contact with nonhairy skin for any length of time.[129] Furthermore, manufacturers recognize the irritation potential of Thioglycolic Acid and its derivatives, and this is specifically addressed in their permanent wave directions and literature:

> Appropriate warnings are provided, including, avoiding eye/skin contact, thoroughly rinsing any accidentally contacted areas, using absorbent material

around the hairline and neck, asking the client if she/he has ever experienced an allergic reaction to a permanent or other cosmetic product (do not give perm, if so), and checking the scalp for sensitivity or any evidence of sores, abrasions, or abnormal condition (if so, do not give perm).[11]

Ammonium Thioglycolate

The skin irritation potential of Ammonium Thioglycolate was evaluated using 39 patients (11 female, 28 male) who had not previously been exposed to cold wave lotions. All subjects were patch tested (48 h exposures) with 0.5 N, 1.0 N, and 1.5 N solutions of Ammonium Thioglycolate. A 1.0 N solution of Ammonium Thioglycolate is approximately 11% Thioglycolate. Faint erythema (1 patient) and erythema (2 patients) were observed at sites patch tested with 1.0 N Ammonium Thioglycolate. The following reactions were observed at sites tested with 1.5 N Ammonium Thioglycolate: faint erythema (1 patient), erythema (1 patient), erythema and edema (1 patient), and erythema and edema + vesicles or papules (3 subjects). Reactions were not noted at sites patch tested with 0.5 N Ammonium Thioglycolate (Table 9).[130]

In another study, Ammonium Thioglycolate (1:100 dilution) was intradermally applied to 14 atopic patients (13–60 years old). Erythema and wheal formation were graded according to the scale: 0 to 4+. The following reactions were observed: 6 patients (4+), 3 patients (3+), 3 patients (2+), and 2 patients (1+) (Table 9).[131]

The skin irritation potential of two permanent waving solutions containing 7.1% Ammonium Thioglycolate, 5.0% urea, and 1.20% ammonium hydroxide was evaluated using 25 subjects (18–65 years old). The solutions were applied via standard or cotton patches to the scapular or interscapular portion of the back. Patches were secured with occlusive tape for 24 h. Reactions were scored 2 to 3 min after patch removal according to the scale: 0 (no reaction) to 4 (intense erythema with edema and vesicles). This procedure was repeated daily (except for Sundays) for a total of 21 consecutive days. Both solutions were classified as strong irritants (Table 9).[132]

Skin irritation was not observed in subjects (number not stated) patch tested with 7.0% Ammonium Thioglycolate (pH 9.6). Patches remained in place for 1 h. In a second experiment, subjects (number not stated) were patch tested with 7.0 and 6.5% Ammonium Thioglycolate solutions. The 7.0% solution (pH 9.6) contained 0.2% dithiodiglycolic acid, and the 6.5% solution (pH 9.4) contained 1.4% dithiodiglycolic acid. Patches made of cotton were saturated with the test solution, covered with a Band-Aid, and enclosed in a watchglass that was sealed in place with tape and collodion. Patches remained in place for 24 h. Skin irritation was not observed in any of the subjects (Table 9).[95]

A 6.5% Ammonium Thioglycolate solution was applied to the skins of 154 subjects daily for a period of 2 months. The duration of each application ranged from 40 to 60 min. Skin irritation was not noted in any of the subjects (Table 9).[55]

Thioglycolic Acid

A lotion base containing 4.5% Thioglycolic Acid was applied to a 2 × 2 cm area on each of 45 patients. Sites were rinsed 10 min later. None of the subjects had signs of inflammation. After a 12-h interval, the lotion was applied to pubic, perineal, and scrotal regions, and sites were rinsed 10 min later. The lotion was not irritating to 33 of the patients. Eleven patients complained of a hot sensation around the scrotum that lasted for only a few minutes (Table 9).[133]

TABLE 9. CLINICAL ASSESSMENT OF SAFETY

Type of study	Test substance	Concentration tested	No. of subjects	Procedure	Results	Reference
Skin irritation	Ammonium Thioglycolate	0.5 to 1.5 N (1.0 N solution yields approx. 11% Thioglycolate)	39 patients	48 h patch test	3 patients with reactions (erythema to 1.0 N solution). 6 patients with reactions (erythema) to 1.5 N solution	130
Skin irritation	Ammonium Thioglycolate	1.0%	14 patients	Intradermal application	Skin irritation in all patients	131
Skin irritation	2 permanent waving solutions (7.1% Ammonium Thioglycolate)	As is	25 subjects	Twenty-one 24 h applications (cotton patches)	Skin irritation in all subjects	132
Skin irritation	Ammonium Thioglycolate	6.5%	154 subjects (76 normal, 78 patients)	40–60 min applications daily for 2 months	No skin irritation reactions	55
Skin irritation	Ammonium Thioglycolate (pH 9.6)	7.0%	Not stated	24 h application (cotton patches)	Nonirritant	95
Skin irritation	Ammonium Thioglycolate (pH 9.4)	6.5%	Not stated	24 h application (cotton patches)	Nonirritant	95
Skin irritation	Ammonium Thioglycolate (pH 9.6)	7.0%	Not stated	1 h application	Nonirritant	95
Skin irritation	Lotion base (4.5% Thioglycolic Acid)	As is	45 patients	10 min application	Nonirritant	133
Skin irritation	Glyceryl Thioglycolate	2.0% aqueous	25 subjects	21 day skin irritation test	Skin irritation in all subjects	136
Skin irritation	Permanent waving solution (14.0–15.4% Glyceryl Thioglycolate; pH 6.5–6.9)	As is	100 subjects	Two 48 h patch applications	No skin irritation reactions	135
Skin irritation and sensitization	Ammonium Thioglycolate (pH 9.3)	≅6.0%	223 patients	48 h induction and 48 h challenge via elastopatches	24 reactions (Exp. 1). 26 immediate reactions, 1 followed by delayed reaction (Exp. 2)	139

Skin irritation and sensitization	Waving lotion (4.61% Thioglycolic Acid and 0.86% Ammonia; pH 9.21)	As is	286 patients	48 h to 7 day patch application (induction and challenge)	No skin irritation or sensitization reactions	130
Skin irritation and sensitization	Ammonium Thioglycolate	18.0%	205 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 96 subjects (induction and/or first challenge)	137
Skin irritation and sensitization	Ammonium Thioglycolate	18.0%	199 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 54 subjects (induction and/or first challenge)	137
Skin irritation and sensitization	Ammonium Thioglycolate	14.4%	220 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 12 subjects (induction), 7 subjects (challenge)	138
Skin irritation and sensitization	Cold wave (9.0% Ammonium Thioglycolate; pH 9.3–9.5)	As is	52 subjects	Repeated insult patch test (semi-occlusive patches)	No skin irritation or sensitization reactions	140
Skin irritation and sensitization	Permanent waving solution (7.1% Ammonium Thioglycolate)	As is	211 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 27 subjects (induction), 19 subjects (induction and challenge), 3 subjects (challenge)	141
Skin irritation and sensitization	Cold wave (17.5% Ammonium Thioglycolate; pH 7.3–7.6)	4.4% Ammonium Thioglycolate	54 subjects	Repeated insult patch test	Irritation or low-grade sensitivity (7 subjects, induction); sensitization (3 subjects, challenge)	142
Skin irritation and sensitization	Cold wave (17.5% Ammonium Thioglycolate; pH 7.3–7.6)	4.4% Ammonium Thioglycolate	102 subjects	Repeated insult patch test	Irritation (20 subjects, induction), irritation or low-grade sensitivity (10 subjects, induction), sensitization (2 subjects, challenge)	143
Skin irritation and sensitization	Permanent waving solution (12% Ammonium Thioglycolate)	0.12% Ammonium Thioglycolate	191 subjects	Repeated insult patch test	Reactions: 5 subjects (induction), 7 subjects (challenge)	144
Skin irritation and sensitization	Glyceryl Thioglycolate	0.25–2.5%	12 patients (8 hairdressers and 4 clients)	48 h application of each conc. via Finn chambers	Positive reactions: 11 patients (1.0% and 2.5% solutions), 9 patients (0.5% solution), 4 patients (0.25% solution)	145

TABLE 9. CLINICAL ASSESSMENT OF SAFETY CONTINUED

Type of study	Test substance	Concentration tested	No. of subjects	Procedure	Results	Reference
Skin irritation and sensitization	Glyceryl Thioglycolate	23.4%	205 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 46 subjects (induction and/or first challenge)	137
Skin irritation and sensitization	Glyceryl Thioglycolate	23.4%	199 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 68 subjects (induction and/or first challenge)	137
Skin irritation and sensitization	Acid wave (22.6% Glyceryl Thioglycolate; pH 6.9–7.2)	As is	101 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 29 subjects (induction), 10 subjects (induction and challenge), 7 subjects (challenge)	146
Skin irritation and sensitization	Acid wave (22.6% Glyceryl Thioglycolate; pH 6.9–7.2)	As is (induction). 2.3% Glyceryl Thioglycolate (induction and challenge)	103 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 6 subjects (22.6% product, induction), 2 subjects (2.3% solution, challenge)	147
Skin irritation and sensitization	Acid wave (22.6% Glyceryl Thioglycolate; pH 6.9–7.2)	As is	52 subjects	Repeated insult patch test (semi-occlusive patches)	No skin irritation or sensitization reactions	148
Skin irritation and sensitization	Glyceryl Thioglycolate	21.6%	52 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 4 subjects (induction), 3 subjects (challenge)	138
Skin irritation and sensitization	Glyceryl Thioglycolate (80.8%)	20.2%	30 subjects	Repeated insult patch test (occlusive patches)	Reactions: 6 subjects (induction), 1 subject (challenge, original site), 1 subject (challenge, adjacent site)	149
Skin irritation and sensitization	Glyceryl Thioglycolate (80.2%)	20.1%	29 subjects	Repeated insult patch test (occlusive patches)	Reactions: 6 subjects (induction), 7 subjects (challenge, original site), 3 subjects (challenge, adjacent site)	149

Skin irritation and sensitization	Glyceryl Thioglycolate	18.0%	55 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 3 subjects (induction), 1 subject (induction and challenge)	138
Skin irritation and sensitization	Acid permanent wave (15.76% Glyceryl Thioglycolate; pH 7.0)	As is (induction 7.88% Glyceryl Thioglycolate (challenge)	193 subjects	Repeated insult patch test (occlusive and semi-occlusive patches)	Reactions: 147 subjects (induction), 76 subjects (induction and challenge), 44 subjects (challenge)	150
Skin irritation and sensitization	Permanent waving lotion (14–15.4% Glyceryl Thioglycolate; pH 6.5–6.9)	As is	103 subjects	Repeated insult patch test (semi-occlusive patches)	No skin irritation or sensitization reactions	135
Skin irritation and sensitization	Glyceryl Thioglycolate	14.4%	55 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 2 subjects (induction), 2 subjects (challenge)	138
Skin irritation and sensitization	Glyceryl Thioglycolate	10.8%	58 subjects	Repeated insult patch test (semi-occlusive patches)	Reactions: 3 subjects (induction), 1 subject (challenge)	138
Skin irritation and sensitization	Acid wave (22.6% Glyceryl Thioglycolate; pH 6.9–7.2)	7.5% Glyceryl Thioglycolate	53 subjects	Repeated insult patch test (semi-occlusive patches)	Low-grade sensitization or cumulative irritation (13 subjects), pre-sensitization (4 subjects), induced contact allergy (10 subjects)	153
Skin irritation and sensitization	Commercial wave 1 (22.0% Glyceryl Thioglycolate)	7.3% Glyceryl Thioglycolate	51 subjects	Repeated insult patch test (occlusive patches)	Low-grade sensitization or cumulative irritation (10 subjects), low-grade sensitization (4 subjects), pre-sensitization (1 subject), induced contact allergy (6 subjects)	153

TABLE 9. CLINICAL ASSESSMENT OF SAFETY *CONTINUED*

Type of study	*Test substance*	*Concentration tested*	*No. of subjects*	*Procedure*	*Results*	*Reference*
Skin irritation and sensitization	Commercial wave 2 (22.0% Glyceryl Thioglycolate)	7.3% Glyceryl Thioglycolate	53 subjects	Repeated insult patch test (occlusive patches)	Low-grade sensitization or cumulative irritation (10 subjects), low-grade sensitization (5 subjects), induced contact allergy (6 subjects)	153
Skin irritation and sensitization	Commercial wave 3 (22.0% Glyceryl Thioglycolate)	7.3% Glyceryl Thioglycolate	53 subjects	Repeated insult patch test (occlusive patches)	Low-grade sensitization or cumulative irritation (6 subjects), low-grade sensitization (16 subjects), pre-sensitization (2 subjects), induced contact allergy (13 subjects)	153
Skin irritation and sensitization	Waving lotion (22.6% Glyceryl Thioglycolate; pH 6.9–7.2)	5.7% Glyceryl Thioglycolate	52 subjects	Repeated insult patch test (occlusive patches)	Reactions: 19 subjects (induction), 12 subjects (challenge, original site), 8 subjects (challenge, new site)	152
Skin irritation and sensitization	Glyceryl Thioglycolate	4% in petrolatum	52 subjects	Repeated insult patch test (occlusive patches)	Reactions: 8 subjects (induction), 16 subjects (induction and challenge), 3 subjects (challenge)	155
Skin irritation and sensitization	Glyceryl Thioglycolate	4% aqueous	51 subjects	Repeated insult patch test (occlusive patches)	Reactions: 11 subjects (induction), 16 subjects (induction and challenge), 10 subjects (challenge)	157

Skin irritation and sensitization	Glyceryl Thioglycolate	2% in petrolatum	51 subjects	Repeated insult patch test (occlusive patches)	Reactions: 9 subjects (induction), 15 subjects (induction and challenge), 4 subjects (challenge)	154
Skin irritation and sensitization	Glyceryl Thioglycolate	2% aqueous	53 subjects	Repeated insult patch test (occlusive patches)	Reactions: 8 subjects (induction), 11 subjects (induction and challenge), 12 subjects (challenge)	156
Skin sensitization	Ammonium Thioglycolate	0.3%–7.0%	19 patients	Closed patch tests	Positive reactions: 5 subjects (3.0% solution), 5 subjects (5.0% solution), 8 subjects (7.0% solution)	73
Skin sensitization	Ammonium Thioglycolate	0.3%–7.0%	19 patients	Open patch tests	Positive reactions: 1 subject (3.0% solution), 1 subject (5.0% solution), 2 subjects (7.0% solution)	73
Skin sensitization	Cold wave (5.0% Ammonium Thioglycolate)	As is	4 patients (hairdressers)	Open patch tests	Positive reactions in all patients	158
Skin sensitization	Ammonium Thioglycolate	5% and 2%	4 patients (hairdressers)	Open patch tests	Positive reactions in all patients	158
Skin sensitization	Ammonium Thioglycolate	2.5% in petrolatum	12 patients (8 hairdressers and 4 clients)	48 h patch application via Finn chamber	Sensitization in 1 subject	145
Skin sensitization	Ammonium Thioglycolate	2.0% and 1.0%	17 patients	Epicutaneous test	Sensitization in 5 patients	105
Skin sensitization	Ammonium Thioglycolate	1.0% and 0.5%	68 patients	Epicutaneous test	Sensitization in 24 patients	105
Skin sensitization	Ammonium Thioglycolate	5%	20 subjects	Open patch tests	No sensitization reactions	158

TABLE 9. CLINICAL ASSESSMENT OF SAFETY *CONTINUED*

Type of study	*Test substance*	*Concentration tested*	*No. of subjects*	*Procedure*	*Results*	*Reference*
Skin sensitization	Ammonium Thioglycolate (pH 9.0–9.3)	1.25%	20 subjects	24 h applications (cotton patches) 3 days/week for 3 weeks. 24 h challenge	No sensitization reactions	114
Skin sensitization	Glyceryl Thioglycolate	2.5%	403 patients	48 h patch applications. Subjects tested over a period of 64 months	Sensitization in 25 patients	159
Skin sensitization	Glyceryl Thioglycolate	2.5% in petrolatum	66 patients (hairdressers)	Patch-tested over a period of 8 years	Allergic reactions in 6 patients	160
Skin sensitization	Glyceryl Thioglycolate	2.5% in petrolatum	7 patients (hairdressers)	Patch-tested over a period of 3 months	Allergic reactions in 5 patients	161
Skin sensitization	Glyceryl Thioglycolate	2.5% in petrolatum	47 subjects	Patch-tested over a period of 3 months	No allergic reactions	161

Glyceryl Thioglycolate

The skin irritation potential of a permanent waving lotion (pH 6.5–6.9) containing 14 to 15.4% Glyceryl Thioglycolate was evaluated according to a modification of the procedure by Schwartz and Peck.[134] A patch containing 0.15 ml of the lotion was applied to the skin of each of 100 subjects and removed after 48 h. Sites were graded for signs of irritation 15 and 24 h after patch removal. After a 14-day nontreatment period, the test procedure was repeated. None of the subjects had signs or symptoms of skin irritation (Table 9).[135]

A 21-day skin irritation test was conducted with 25 subjects. Each subject was patch tested with an aqueous solution of 2.0% Glyceryl Thioglycolate. Intense erythema with edema and vesicles were observed in all subjects during the first 10 days of testing. Ten days after completion of the test, each subject received a single challenge application of the test substance. Positive reactions were noted in all subjects. Most of these were irritation reactions. However, some appeared to be allergic in nature. Biopsies (at reaction site) were performed on some of the subjects with allergic reactions. The cutaneous alterations were as follows: focal spongiosis and reticular degeneration of the epidermis and scattered intraepidermal accumulations of neutrophils. These results are compatible with irritant contact dermatitis (Table 9).[136]

Mucous Membrane Irritation

Ammonium Thioglycolate

Fourteen asthmatic patients (13–60 years old) inhaled mists of the following dilutions of Ammonium Thioglycolate: 1:10, 1:100, 1:10,000, and 1:100,000. After exposure, 13 patients had the following signs and symptoms: asthmatic breathing, an uncontrollable paroxysmal cough, pharyngeal irritation, and blocked nasal passages or nasal drip. Pharyngeal irritation lasted 0.5 to 2 h, depending on the degree of sensitivity of the patient. Eight control patients (nonasthmatic and nonatopic) did not have positive reactions to the test substance.[131]

Skin Irritation and Sensitization

Ammonium Thioglycolate

The skin irritation and sensitization potentials of 18.0% Ammonium Thioglycolate were evaluated in a modified repeated insult patch test using 220 healthy subjects (25 males, 195 females, 18–66 years old). These subjects were also simultaneously patch tested with 23.4% Glyceryl Thioglycolate, and the results are summarized later in this section on Skin Irritation and Sensitization. None of the subjects had ever been patch tested with hair permanent products, and all were instructed not to have their hair permed during the entire course of the study. Any subject who had his or her hair permed within 2 weeks before participation in the study or who was sensitive to hair permanent products was disqualified. The test substance (0.2 ml) was applied to the back of each subject in the area between scapulae and waist adjacent to the midline, via a 2 cm × 2 cm patch affixed to semiocclusive tape. A new site was used for each induction patch. Applications were made on Mondays, Wednesdays, and Fridays for a total of nine 24 h applications. Patch removals on Tuesdays and Thursdays were each followed by a 24 h nontreatment period, and those on Saturday by a 48 h nontreatment period. Reactions at each site were scored prior to the next patch application according

to the scale: 0 (no evidence of any effect) to 4 (deep-red erythema with/without vesiculation or weeping). After a 12 to 14-day nontreatment period, a challenge patch was applied for 24 h to a new test site on each subject. Reactions generally were scored at 24 and 48 h postapplication. Three of the original 220 subjects were disqualified because of reactions, severer than mild erythema, to one or both test substances during the first three inductions, and 12 subjects withdrew from the study for personal reasons that were unrelated to the conduct of the study. Of the 205 subjects who completed the study, barely perceptible to mild, nonspecific erythema and/or low to moderate-grade erythema was observed in 96 subjects during induction and/or the first challenge phase of the study. During the first challenge, 6 subjects had reactions that were classified as mild erythema (score = 1), and 1 subject had moderate erythema (score = 2). Reactions severer than moderate erythema were not observed. These 7 subjects were selected for the second challenge; 4 subjects declined to participate. After the second challenge, 1 subject had no reactions, and another subject had barely perceptible erythema at 24 h but not at 48 h postapplication. The third subject had no reactions at 24 h, barely perceptible erythema at 48 h, and latent, moderate erythema at 72 h postapplication. The authors concluded that 18.0% Ammonium Thioglycolate was a very mild to moderate irritant in approximately 47% (96/205) of the population tested and that the results of initial challenge patch testing of 205 subjects and a second challenge patch test involving 3 subjects did not indicate any evidence of induced allergic contact dermatitis (Table 9).[137]

In another study, the skin irritation and sensitization potentials of 18.0% Ammonium Thioglycolate were evaluated in a modified repeated insult patch test using 220 healthy subjects (24 males, 196 females, 18–69 years old). These subjects also were simultaneously patch tested with 23.4% Glyceryl Thioglycolate, and the results are summarized later in this section on Skin Irritation and Sensitization. None of the subjects had ever been patch tested with hair permanent products, and all were instructed not to have their hair permed during the entire course of the study. Any subject who had his or her hair permed within 2 weeks before participation in the study or who was sensitive to hair permanent products was disqualified. The test substance (0.2 ml) was applied to the upper outer arm of each subject via a 2 cm × 2 cm patch affixed to semi-occlusive tape. The same site was used for each induction patch, and was rinsed prior to each application. Applications were made on Mondays, Wednesdays, and Fridays for a total of nine 5 h applications. Patch removals on Mondays and Wednesdays were each followed by a 43 h nontreatment period, and those on Friday, by a 67 h nontreatment period. Reactions at each site were scored prior to the next patch application according to the scale: 0 (no evidence of any effect) to 4 (deep-red erythema with/without vesiculation or weeping). After a 12 to 14-day nontreatment period, a challenge patch was applied for 24 h to a new test site on each subject. Reactions generally were scored at 24 and 48 h postapplication. A total of 199 of the original 220 subjects completed the test procedure. Two subjects were disqualified because of reactions to one or both test substances, after the first three inductions, that were more severe than mild erythema. One subject withdrew because of a reaction, barely perceptible erythema, that was accompanied by burning and itching, and 18 subjects withdrew because of personal reasons that were unrelated to the conduct of the study. Of the 199 subjects who completed the study, 54 had barely perceptible to marked erythema during induction and/or the first challenge phase. During the first challenge, 3 subjects had reactions that were classified as mild erythema (score = 1), and 1 subject had mild and moderate erythema (score = 2). Reactions severer than moderate

erythema were not observed. These 4 subjects were selected for a second challenge; 1 did not participate because of widespread dermatitis. The reactions observed after the second challenge were as follows: 1 subject with barely perceptible erythema at 24 and 48 h postapplication and moderate erythema and edema at 72 h, 1 subject with no reactions at 24 and 48 h and barely perceptible erythema at 72 h, and 1 subject with no reactions at 24 h, 48 h, or 72 h. The authors concluded that 18.0% Ammonium Thioglycolate induced very mild to marked irritation in approximately 27% (54/199) of the population tested and that the results of initial repeated insult patch testing of the 199 subjects and a second challenge patch test involving 3 subjects suggested that 2 subjects had possible low-grade, nonpersistent irritant reactivity and 1 subject had probable moderate-grade induced allergic contact dermatitis (Table 9).[137]

Repeated insult patch tests were used to evaluate the skin irritation and sensitization potential of 14.4% Ammonium Thioglycolate and 10.8%, 14.4%, 18.0%, and 21.6% Glyceryl Thioglycolate in a total of 240 subjects (32 males, 208 females, 18–69 years old). A panel of 240 subjects was patch tested with 14.4% Ammonium Thioglycolate, and four goups of 60 subjects (same 240 subjects) were patch tested with 10.8%, 14.4%, 18.0%, and 21.6% Glyceryl Thioglycolate, respectively. The results for subjects patch tested with these concentrations of Glyceryl Thioglycolate are included in this section under the heading, 'Glyceryl Thioglycolate.' On Mondays, Wednesdays, and Fridays, the test substance was applied (0.2 ml, semi-occlusive patch) for 24 h to an area, between the scapulae and waist, adjacent to the midline. New sites were used for subsequent induction patch applications. Patch removals on Tuesday and Thursday were each followed by a 24 h nontreatment period, and removals on Saturday by a 48 h nontreatment period. Each site was scored prior to application of the next patch according to the scale: 0 (no evidence of any effect) to 4 (severe, defined as deep-red erythema with/without vesiculation or weeping). The test procedure was repeated for a total of nine applications. After a 15 to 19 day nontreatment period, challenge patches were applied to new test sites. Reactions were scored at 24 and 48 h postapplication. Any subject with a reaction during the challenge phase that was stronger than mild erythema (score = 1) was rechallenged 28 days later at a new test site. A total of 20 subjects withdrew from the study, during induction phase, for reasons that were unrelated to treatment. Four of the subjects who withdrew had reactions to 14.4% Ammonium Thioglycolate: barely perceptible erythema (2 subjects), mild erythema with mild edema (1 subject), and moderate erythema (1 subject). Of the 220 subjects who completed the study, 4 were not available for 24 h challenge readings. In these subjects, reactions were not observed during 48 h challenge readings nor during the induction phase. Twelve of the 220 subjects had reactions to 14.4% Ammonium Thioglycolate only during the induction phase. Reactions classified as barely perceptible erythema (score = +) predominated. Stronger reactions were observed in 3 subjects: 1 subject with mild erythema (score = 1) and 2 subjects with moderate erythema (score = 2). Reactions to not more than two induction applications were observed. Seven subjects had reactions to 14.4% Ammonium Thioglycolate only during the challenge phase. Reactions classified as barely perceptible erythema predominated. A stronger reaction, moderate erythema with mild edema (score = 2e; 48 h reading), was observed in 1 subject. Reactions were not observed after the second challenge. The authors concluded that 14.4% Ammonium Thioglycolate did not induce clinically meaningful irritation or any evidence of induced allergic contact dermatitis in human subjects (Table 9).[138]

A group of 223 subjects (18–34 years old, normal skin) was patch tested with 0.55

N Ammonium Thioglycolate (≈6.0% solution, pH 9.3). Sixty-five subjects had histories of dermatitis due to contact with plants, and 21 subjects had histories of other types of cutaneous disturbances. Also, 101 subjects had previously used cold wave formulations. The test solution was applied via elastopatches to the inner surface of the right arm and to a similar site on the left arm. Patches were removed at 48 h postapplication, and sites were graded. Sites also were graded approximately every 48 h thereafter. Patches were reapplied to the same sites 2 weeks after the first application. Reactions to Ammonium Thioglycolate were observed in 24 subjects. Of the 213 subjects retested with 0.55 N Ammonium Thioglycolate (same procedure), 26 had an immediate reaction. One of the 26 subjects had a delayed reaction. It was concluded that 0.55 N Ammonium Thioglycolate induced skin irritation and sensitization (Table 9).[139]

Two hundred eighty-six patients (143 males, 143 females) were patch tested with a hair waving lotion (pH 9.21) containing 0.86% ammonia and 4.61% Thioglycolic Acid. Patches remained in place for periods ranging from 48 h to 7 days. Most of the patients had not been exposed previously to ingredients of cold wave formulations. Of the patients tested, 63 and 61 had fungal infections and eczematous dermatitis, respectively. The remaining 162 patients were described as having miscellaneous skin conditions. Skin irritation was not observed in any of the 286 patients tested. When patch tests were repeated (109 patients) 20 to 40 days later, sensitization reactions were not observed (Table 9).[130]

In another study, 863 subjects were patch tested with a hair waving lotion (same as above) containing 0.86% ammonia and 4.61% Thioglycolic Acid. Of these subjects, 140 had diseased skin, whereas the remaining subjects were normal. Reactions (types not stated) to the wave formulation were observed in 16 subjects, 5 of whom had a history of skin disorders that were not due to contact with waving lotions. When 15 of the subjects were retested, 2 had reactions that were definitely positive. Prior to testing, these 2 subjects had had five and three cold waves, respectively.[130]

The skin irritation and sensitization potentials of a cold wave product (pH 9.3–9.5) containing 9.0% Ammonium Thioglycolate were evaluated using 52 subjects (29–77 years old) according to the Draize-Shelanski repeated insult patch test. Nine induction patch (semi-occlusive) applications of the product were made to the upper back of each subject during 21 consecutive days. Each patch remained in place for 23 h, after which sites were scored according to the scale: 0 (no reaction) to 4 (severe erythema to slight eschar formation; severe edema). Challenge patches were applied (new sites) 12 days after application of the last induction patch, and each patch remained in place for 23 h. Sites were scored (same scale) 48 and 72 h after application. Reactions to the product were not observed at any time during the study. The product was neither an irritant nor a sensitizer (Table 9).[140]

The skin irritation and sensitization potentials of a permanent waving solution containing 7.1% Ammonium Thioglycolate, 5.0% urea, and 1.20% ammonium hydroxide were evaluated, using 211 subjects, according to the procedure stated immediately above. Reactions were observed in 48 subjects: 27 subjects (induction phase), 19 subjects (induction and challenge phases), and 3 subjects (challenge phase). Reactions ranged from mild erythema to intense erythema with edema and formation of vesicles during the induction phase and from mild erythema to intense erythema with edema during the challenge phase (Table 9).[141]

In another study, the skin irritation and sensitization potential of a 25.0% aqueous

solution of a cold wave containing 17.5% Ammonium Thioglycolate (pH 7.3–7.6; effective concentration of Ammonium Thioglycolate 4.4%) were evaluated using 54 subjects (18–67 years old). The solution was applied for 24 h either to the inner aspect of the arm or to the back, via an occlusive patch. A total of 10 applications was made to each subject. Patch removals on Tuesdays and Thursdays were each followed by a 24 h nontreatment period. Patch removals on Saturdays were each followed by a 48 h nontreatment period. Sites were scored during nontreatment periods according to the scale: 0 (no reaction) to 4 (deep red erythema with vesiculation or weeping). Ten to 18 days after application of the last induction patch, challenge patches were applied to original and adjacent sites for 24 h. Sites were scored (same scale) 24 and 48 h after application. During induction, erythema (pink to bright red) was observed in 7 subjects. These reactions were not observed during the challenge phase and, therefore, were classified as either cumulative irritant effects or low-grade sensitivity. Reactions indicative of allergic contact sensitization were observed in 3 subjects during the challenge phase: pink, uniform erythema (1 subject; original and adjacent sites), pink-red to bright red erythema (1 subject; adjacent site), and pink-red erythema (1 subject; adjacent site). The 3 subjects with reactions during the challenge phase, as well as 16 of the subjects who did not have reactions, were rechallenged with a 20.0% solution of the cold wave (effective concentration of Ammonium Thioglycolate 3.5%). Subjects with and without reactions were rechallenged after 4 and 8 week nontreatment periods, respectively. Of the 3 subjects tested, reactions indicative of allergic contact sensitization were observed in 1 subject. Two of the 16 subjects had minimal erythema and pink uniform erythema, respectively (Table 9).[142]

The skin irritation and sensitization potentials of another cold wave product (pH 7.3–7.6) containing 17.5% Ammonium Thioglycolate were evaluated using 102 subjects (15–73 years old) according to the procedure stated immediately above. The product was tested at a concentration of 25% (effective concentration of Ammonium Thioglycolate 4.4%) in distilled water. During induction, erythema (pink to pink-red) was observed in 20 subjects. These reactions were not observed during the challenge phase and, therefore, were classified as low-level cumulative irritation. Induction reactions (pink to pink-red erythema) classified either as cumulative irritation or low-grade sensitivity were observed in 10 subjects. This classification was based on additional observations of minimal erythema or erythema (pink appearance) during the challenge phase. Reactions suggestive of moderate allergic contact sensitization (pink-red to bright red erythema) were observed in 2 subjects during the challenge phase (Table 9).[143]

The skin irritation and sensitization potentials of a permanent waving solution containing 12.0% Ammonium Thioglycolate, 5.0% urea, and 0.61% ammonium hydroxide were evaluated according to a modification of the Draize-Shelanski-Jordan patch test. A total of 191 subjects (139 females, 52 males) was tested. The product was diluted to a 1.0% solution (effective concentration of Ammonium Thioglycolate 0.12%) and applied to the back via an occlusive patch on alternate days for a total of ten 24 h applications. After a 13 day nontreatment period, a challenge patch was applied for 48 h to the back of each subject. A second challenge patch was applied (48 h contact period) 7 days later. Challenge sites were scored 48 and 72 h after application. Reactions were scored according to the scale: 0 (no reaction) to 4 (intense erythema with edema and vesicles). The following rections were observed: mild erythema (3

subjects, induction; 7 subjects, challenge), intense erythema (1 subject, induction) and mild erythema to intense erythema with edema (1 subject, induction). The product was neither an irritant nor an allergen when diluted to a concentration of 1% (Table 9).[144]

Glyceryl Thioglycolate

Eight hairdressers (average age 31) and 4 clients (average age 57) developed allergic reactions to a permanent wave formulation containing Glyceryl Thioglycolate. Dermatitis was noted on the fingers of hairdressers and on the neck, ears, and scalp of clients. The hairdressers had been exposed to the wave formulation for a period of 1 to 21 months and clients for a period of 1.5 to 4 years. Seven of the hairdressers and 1 client had personal histories of atopy (asthma, hay fever, or eczema). The 12 patients (hairdressers and clients) were patch tested (Finn chambers) over a period of 30 months with concentrations of Glyceryl Thioglycolate ranging from 0.25 to 2.5%. Finn chambers remained in place for 48 h. Sites were graded 30 min and 7 days after patch removal. Only rections observed in a subject during both grading sessions were considered positive. The distribution of positive reactions was as follows: 11 patients (2.5% Glyceryl Thioglycolate), 11 patients (1.0% Glyceryl Thioglycolate), 9 patients (0.5% Glyceryl Thioglycolate), and 4 patients (0.25% Glyceryl Thioglycolate). Results for the twelfth patient were not included. Irritant reactions were observed in 1 of 45 control subjects patch tested with 2.5% Glyceryl Thioglycolate. In a second control group (60 subjects), there were no irritant reactions to 1.0% Glyceryl Thioglycolate (Table 9).[145]

The skin irritation and sensitization potentials of 23.4% Glyceryl Thioglycolate were evaluated in a modified repeated insult patch test using 220 healthy subjects (25 males, 195 females, 18–66 years old). These subjects also were patch tested simultaneously with 18.0% Ammonium Thioglycolate, and the results are summarized earlier in this section on Skin Irritation and Sensitization. None of the subjects had ever been patch tested with hair permanent products, and all were instructed not to have their hair permed during the entire course of the study. Any subject who had his or her hair permed within 2 weeks before participation in the study or who was sensitive to hair permanent products was disqualified. The test substance (0.2 ml) was applied to the back of each subject, area between scapulae and waist adjacent to the midline, via a 2 cm × 2 cm patch affixed to semi-occlusive tape. A new site was used for each induction patch. Applications were made on Monday, Wednesday, and Friday for a total of nine 24 h applications. Patch removals on Tuesdays and Thursdays were each followed by a 24 h nontreatment period, and those on Saturday, by a 48 h nontreatment period. Reactions at each site were scored prior to the next patch application according to the scale: 0 (no evidence of any effect) to 4 (deep-red erythema with/without vesiculation or weeping). After a 12 to 14 day nontreatment period, a challenge patch was applied for 24 h to a new test site on each subject. Reactions generally were scored at 24 and 48 h postapplication. Three of the original 220 subjects were disqualified because of reactions, severer than mild erythema, to one or both test substances during the first three inductions, and 12 subjects withdrew from the study for personal reasons that were unrelated to the conduct of the study. Of the 205 subjects who completed the study, barely perceptible to mild, nonspecific and/or low to moderate-grade erythema was obscured in 46 subjects during the induction and/or the first challenge phase of the study. During the first challenge, 2 subjects had rections that were classified as mild erythema (score = 1). Reactions severer than mild erythema were not observed. These

2 subjects were selected for the second challenge; 1 subject declined to participate. After the second challenge, mild erythema was observed at 24 h postapplication, and no rections were observed at 48 h. The authors concluded that 23.4% Glyceryl Thioglycolate was a very mild to moderate irritant in approximately 22% (46/205) of the population tested and that the results of initial challenge patch testing of 205 subjects and a second challenge patch test involving 1 subject did not indicate any evidence of induced allergic contact dermatitis (Table 9).[137]

In another study, the skin irritation and sensitization potentials of 23.4% Glyceryl Thioglycolate were evaluated in a modified repeated insult patch test using 220 subjects (24 males, 196 females, 18–69 years old). These subjects were also simultaneously patch tested with 18.0% Ammonium Thioglycolate, and the results are summarized earlier in this section on Skin Irritation and Sensitization. None of the subjects had ever been patch tested with hair permanent products, and all were instructed not to have their hair permed during the entire course of the study. Any subject who had his or her hair permed within 2 weeks before participation in the study or who was sensitive to hair permanent products was disqualified. The test substance (0.2 ml) was applied to the upper outer arm of each subject via a 2 cm × 2 cm patch affixed to semi-occlusive tape. The same site was used for each induction patch and was rinsed prior to each application. Applications were made on Mondays, Wednesdays, and Fridays for a total of nine 5 h applications. Patch removals on Mondays and Wednesdays were each followed by a 43 h nontreatment period, and those on Friday, by a 67 h nontreatment period. Reactions at each site were scored prior to the next patch application according to the scale: 0 (no evidence of any effect) to 4 (deep-red erythema with/without vesiculation or weeping). After a 12 to 14 day nontreatment period, a challenge patch was applied for 24 h to a new test site on each subject. Reactions generally were scored at 24 h and 48 h postapplication. A total of 199 of the original 220 subjects completed the test procedure. Two subjects were disqualified because of reactions to one or both test substances, after the first three inductions, that were severer than mild erythema. One subject withdrew because of a reaction, barely perceptible erythema that was accompanied by burning and itching, and 18 subjects withdrew because of personal reasons that were unrelated to the conduct of the study. Of the 199 subjects who completed the study, 68 had barely perceptible to marked erythema during induction and/or the first challenge phase. During the first challenge, 5 subjects had rections that were classified as mild erythema (score = 1), 1 subject had mild and moderate erythema (score = 2), and 1 subject had moderate erythema. Reactions severer than moderate erythema were not observed. These 7 subjects were selected for a second challenge; 1 subject did not participate because of widespread dermatitis. The following reactions (6 subjects) were observed during the second challenge: 1 subject with moderate erythema and mild edema at 24 h postapplication, mild erythema with mild edema at 48 h, and no rections at 72 h; 1 subject with mild erythema at 24 h, mild erythema with mild edema at 48 h, and moderate erythema with mild edema at 72 h; 1 subject with moderate erythema and mild edema at 24 and 48 h and mild erythema with mild edema at 72 h; 1 subject with nonerythematous papular eruptions at 24, 48, and 72 h; 1 subject with no reactions at 24 h and barely perceptible erythema at 48 and 72 h; 1 subject with transient, mild erythema with papular eruptions at 48 h and papules and no erythema at 72 h. The authors concluded that 23.4% Glyceryl Thioglycolate induced very mild to marked skin irritation in approximately 34% (68/199) of the population tested. Also, the results of initial repeated insult patch testing of the 199 subjects and the second challenge patch test involving 6 subjects suggested that 4

subjects (4/199) had possible low to moderate-grade irritant sensitivity and that 2 subjects had possible and probable moderate-grade induced allergic contact dermatitis, respectively (Table 9).[137]

The skin irritation and sensitization potentials of an acid wave product (pH 6.9–7.2) containing 22.6% Glyceryl Thioglycolate were evaluated, using 101 subjects, according to a modification of the Draize-Shelanski-Jordan repeated insult patch test. The product was applied to the back of each subject via a semi-occlusive patch for 24 h. Sites were then scored during a 24 h nontreatment period according to the scale: 0 (no reaction) to 4 (intense erythema with edema and vesicles). This procedure was repeated on Monday through Friday for a total of 10 induction applications. After a 2 week nontreatment period, the first challenge patch was applied for 48 h. The second challenge patch was applied (48 h period) 1 week after application of the first. Sites were scored (same scale) immediately after patch removal. A total of 46 subjects had reactions to the product. Reactions ranging from mild erythema to intense erythema with edema and vesicles were observed in 39 subjects. Twenty-nine of these subjects had reactions only during the induction phase, and 10 subjects had reactions during induction and challenge phases. Seven subjects had reactions, mild erythema to intense erythema with edema, only during the challenge phase (Table 9).[146]

The skin irritation and sensitization potentials of the acid wave product (22.6% Glyceryl Thioglycolate) mentioned in the preceding study also were evaluated using the repeated insult semi-occlusive patch test. A total of 103 subjects were tested (18–74 years old). The product was applied for 24 h to the back (between scapulae and waist) of each subject. Patch removals on Tuesdays and Thursdays were followed by 24 h nontreatment periods. Patch removals on Saturdays were followed by 48 h nontreatment periods. Sites were scored prior to the next patch application according to the scale: 0 (no reaction) to 4 (deep-red erythema with vesiculation or weeping). This procedure was repeated for a total of nine applications. After a 12 to 17 day nontreatment period, challenge patches were applied to new sites. Sites were scored (same scale) 24 and 48 h after application. Because of moderate irritation, excessive drying of certain test sites, and 2 subjects with mild to moderate presensitization responses during the first and second inductions, the concentration tested was reduced from full strength to 10% (effective concentration of Glyceryl Thioglycolate 2.3%) during the third through ninth inductions and during the challenge. Mild to moderate irritant or cumulative irritant reactions were observed in 6 subjects during the first and second inductions when the product was tested full strength. Skin irritation was not observed after the concentration was reduced to 10%. Mild to moderate presensitization reactions were observed in 2 subjects after removal of the first induction patch. These 2 subjects also had moderate to marked erythematous reactions and mild edema 48 h after application of the challenge patch. The product did not induce allergic contact dermatitis in any of the subjects (Table 9).[147]

The skin irritation and sensitization potentials of another acid wave product (pH 6.9–7.2) containing 22.6% Glyceryl Thioglycolate were evaluated using 52 subjects (29–77 years old) according to the Draize-Shelanski repeated insult patch test. Nine induction patch (semi-occlusive) applications of the product were made to the upper back of each subject during 21 consecutive days. Each patch remained in place for 23 h, after which sites were graded according to the scale: 0 (no reaction) to 4 (severe erythema to slight eschar formation; severe edema). Challenge patches were applied (new sites) 12 days after application of the last induction patch, and each patch

remained for 23 h. Sites were scored (same scale) 48 and 72 h after application. Reactions to the product were not observed at any time during the study. The product was neither an irritant nor a sensitizer (Table 9).[148]

A repeated insult patch test was used to evaluate the skin irritation and sensitization potential of 21.6% Glyceryl Thioglycolate in a total of 60 subjects (18–69 years old). These subjects were also patch tested with 14.4% Ammonium Thioglycolate (see under the heading, 'Ammonium Thioglycolate' in this section). On Mondays, Wednesdays, and Fridays, the test substance was applied (0.2 ml semi-occlusive patch) for 24 h to an area, between the scapulae and waist, adjacent to the midline. New sites were used for subsequent induction patch applications. Patch removals on Tuesday and Thursday were each followed by a 24 h nontreatment period, and removals on Saturday was followed by a 48 h nontreatment period. Each site was scored prior to application of the next patch according to the scale: 0 (no evidence of any effect) to 4 (severe, defined as deep-red erythema with/without vesiculation or weeping). The test procedure was repeated for a total of nine applications. After a 15 to 19 day nontreatment period, challenge patches were applied to new test sites. Reactions were scored at 24 and 48 h postapplication. Any subject with a reaction during the challenge phase that was stronger than mild erythema (score = 1) was rechallenged 28 days later at a new test site. A total of 8 subjects withdrew from the study during the induction phase for reasons that were unrelated to treatment. Three of the subjects who withdrew had reactions that were classified as barely perceptible erythema. Four of the 52 subjects who completed the study had rections to 21.6% Glyceryl Thioglycolate only during the induction phase. Barely perceptible erythema (score = +) was observed in 3 subjects, and mild erythema (score = 1) was observed in 1 subject. Reactions to not more than two induction applications were observed. Three subjects had reactions, barely perceptible erythema (24 h reading), only during the challenge phase. The authors concluded that 21.6% Glyceryl Thioglycolate did not induce clinically meaningful irritation nor any evidence of induced allergic contact dermatitis in human subjects (Table 9).[138]

In another study, the skin irritation and sensitization potentials of a 25.0% aqueous solution of 80.2% Glyceryl Thioglycolate (effective concentration of Glyceryl Thioglycolate 20.1%) were evaluated using 29 subjects (14–74 years old). The solution was applied, either to the inner aspect of the arm or to the back (between scapulae and waist), for 24 h via an occlusive patch. Ten applications were made to each subject. Patch removals on Tuesdays and Thursdays were each followed by a 24 h nontreatment period. Patch removals on Saturdays were each followed by a 48 h nontreatment period. Sites were scored during nontreatment periods according to the scale: 0 (no reaction) to 4+ (erythema, papules, marked edema, and vesicles). Ten to 14 days after application of the last induction patch, challenge patches were applied to original and adjacent sites for 24 h. Sites were scored (same scale) 24 and 48 h after application. During the induction phase, reactions (6 subjects) ranging from 1+ (erythema) to 3+ (erythema, papules or mild edema, and vesicles) were observed. During the challenge phase, reactions (1+ and 2+) were observed at original sites in 7 subjects. Only 3 subjects had reactions at previously untreated sites. When 19 subjects were rechallenged with the solution at approximately 3 weeks after completion of the test, no reactions were observed. Only 2 of the subjects with reactions during the initial challenge were available for the rechallenge. The authors concluded that the solution was capable of inducing sensitization but not irritation after repeated applications. A similar conclusion was reached when a 25% aqueous solution of 80.8% Glyceryl

Thioglycolate (effective concentration of Glyceryl Thioglycolate 20.2%) was applied (same procedure) to 30 subjects (12–60 years old) (Table 9).[149]

A repeated insult patch test was used to evaluate the skin irritation and sensitization potential of 18.0% Glyceryl Thioglycolate in a total of 60 subjects (18–69 years old). These subjects were also patch tested with 14.4% Ammonium Thioglycolate (see under the heading 'Ammonium Thioglycolate' in this section). On Mondays, Wednesdays, and Fridays, the test substance was applied (0.2 ml, semi-occlusive patch) for 24 h to an area, between the scapulae and waist, adjacent to the midline. New sites were used for subsequent induction patch applications. Patch removals on Tuesday and Thursday were each followed by a 24 h nontreatment period, and removals on Saturday by a 48 h nontreatment period. Each site was scored prior to application of the next patch according to the scale: 0 (no evidence of any effect) to 4 (severe, defined as deep-red erythema with/without vesiculation or weeping). The test procedure was repeated for a total of nine applications. After a 15 to 19 day nontreatment period, challenge patches were applied to new test sites. Reactions were scored at 24 and 48 h postapplication. Any subject with a reaction during the challenge phase that was stronger than mild erythema (score = 1) was rechallenged 28 days later at a new test site. A total of 5 subjects withdrew from the study during the induction phase for reasons that were unrelated to treatment. None of the subjects who withdrew had reactions. Three of the 55 subjects who completed the study had rections, barely perceptible erythema (score = +), to 18.0% Glyceryl Thioglycolate only during the induction phase. Reactions to not more than two induction applications were observed. One subject had a reaction, barely perceptible erythema, to one induction application of 18.0% Glyceryl Thioglycolate, mild erythema (score = 1, 48 h reading) during the first challenge and barely perceptible erythema (24 h reading) during the second challenge. The authors concluded that 18.0% Glyceryl Thioglycolate induced neither clinically meaningful irritation nor any evidence of induced allergic contact dermatitis in human subjects (Table 9).[138]

The modified Draize-Shelanski-Jordan repeat insult patch test was used to evaluate the skin irritation and sensitization potentials of an acid permanent waving solution containing 15.76% Glyceryl Thioglycolate (pH 7.0). A total of 193 subjects completed the study. The solution (2 μl) was applied initially to the back of each subject via an occlusive patch for a period of 24 h. Reactions were scored immediately after patch removal according to the scale: 0 (no rections) to 4 (intense erythema with edema and vesicles). This procedure was repeated on Monday through Friday for a total of ten induction applications. Because of numerous irritation reactions, applications subsequent to the third were made via semi-occlusive patches. The induction phase was followed by a 2 week nontreatment period, after which a challenge patch was applied to each subject (new site) for 48 h. Each challenge patch was moistened with a 50% dilution of the waving solution (effective concentration of Glyceryl Thioglycolate 7.88%). A second challenge patch was applied (48 h period) 1 week after application of the first. Reactions to the first challenge were scored (same scale) immediately after patch removal. Reactions to the second challenge were scored immediately after patch removal and 24 h later. A total of147 subjects had reactions to the waving solution: 27 subjects (induction phase only), 76 subjects (induction and challenge phases), and 44 subjects (challenge phase only). Mild and intense erythematous reactions predominated during both phases. The waving solution was classified as an irritant (Table 9).[150]

The skin irritation and sensitization potentials of a permanent waving lotion (pH

6.5–6.9) containing 14 to 15.4% Glyceryl Thioglycolate were evaluated according to a modification of the procedure by Marzulli and Maibach.[151] A semi-occlusive patch containing 0.5 ml of the lotion was applied to each of 103 subjects. After 48 h of contact, patches were removed and sites were scored for signs of irritation. This procedure was repeated for a total of ten 48 h exposures. After a 14 day nontreatment period, a challenge patch was applied (48 h exposure) to each subject. Sites were then scored. The lotion induced neither irritation nor sensitization in any of the subjects (Table 9).[135]

A repeated insult patch test was used to evaluate the skin irritation and sensitization potential of 14.4% Glyceryl Thioglycolate in a total of 60 subjects (18–69 years old). These subjects were also patch tested with 14.4% Ammonium Thioglycolate (see under the heading 'Ammonium Thioglycolate' in this section). On Mondays, Wednesdays, and Fridays, the test substance was applied (0.2 ml, semi-occlusive patch) for 24 h to an area between the scapulae and waist, adjacent to the midline. New sites were used for subsequent induction patch applications. Patch removals on Tuesday and Thursday were each followed by a 24 h nontreatment period, and removals on Saturday by a 48 h nontreatment period. Each site was scored prior to application of the next patch according to the scale: 0 (no evidence of any effect) to 4 (severe, defined as deep-red erythema with/without vesiculation or weeping). The test procedure was repeated for a total of nine applications. After a 15 to 19 day nontreatment period, challenge patches were applied to new test sites. Reactions were scored at 24 and 48 h postapplication. Any subject with a reaction during the challenge phase that was stronger than mild erythema (score = 1) was rechallenged 28 days later at a new test site. A total of 5 subjects withdrew from the studies during induction for reasons that were unrelated to treatment. None of the subjects who withdrew had reactions. Of the 55 subjects who completed the study, 3 were not available for 24 h challenge readings. In these subjects, reactions were not observed during 48 h challenge readings nor during the induction phase. Two of the 55 subjects had rections, barely perceptible erythema (score = +), to 14.4% Glyceryl Thioglycolate only during the induction phase. Reactions to one induction application were observed. Additionally, 2 subjects had rections only during the challenge phase. One subject had barely perceptible erythema (24 h reading), and the second subject had moderate erythema with mild to moderate edema (score = 2e, 24 h reading), marked erythema with mild to moderate edema and papules (score = 3ep, 48h reading), and severe erythema with mild to moderate edema (score = 4e, 72h reading). During the second challenge, this subject had severe erythema with mild to moderate edema (score = 4e, 24 and 48 h readings) and marked erythema with mild to moderate edema (score = 3e, 72 h reading). The authors concluded that 14.4% Glyceryl Thioglycolate did not induce irritant reactivity but did induce allergic contact dermatitis in 1 of 55 subjects (Table 9).[138]

In another study, the skin irritation and sensitization potentials of 10.8% Glyceryl Thioglycolate were evaluated using 60 subjects (18–69 years old) according to the procedure in the preceding paragraph. These subjects were also patch tested with 14.4% Ammonium Thioglycolate (see under the heading 'Ammonium Thioglycolate' in this section). Two subjects withdrew from the study during induction for reasons that were unrelated to treatment. One of the subjects who withdrew had a reaction that was classified as mild erythema. Of the 58 subjects who completed the study, 1 was not available for the 24 h challenge reading. In this subject, reactions were not observed during the 48 h challenge reading nor during the induction phase. Three of the 58

subjects had reactions to 10.8% Glyceryl Thioglycolate only during the induction phase. Reactions to not more than three induction applications were observed. Mild erythema (score = 1) was observed in 1 subject, and moderate erythema (score = 2) in 2 subjects. One subject had a reaction, barely perceptible erythema (score = +, 24h reading) only during the challenge phase. The authors concluded that 10.8% Glyceryl Thioglycolate did not induce clinically meaningful irritation or any evidence of induced allergic contact dermatitis in human subjects (Table 9).[138]

The skin irritation and sensitization potentials of a waving lotion (pH 6.9–7.2) containing 22.6% Glyceryl Thioglycolate were evaluated using 52 subjects (12–68 years old). A 25% aqueous solution of the lotion (effective concentration of Glyceryl Thioglycolate 5.7%) was applied to each subject via occlusive patches according to a repeated insult patch test procedure.[149] During the induction phase, reactions to the solution were observed in 19 subjects; 1+ (erythema) and 2+ (erythema and papules) reactions predominated. Twelve subjects had reactions, mostly 1+ and 2+ (original sites), during the challenge phase. Reactions (previously untreated sites) were observed in 8 subjects. The authors concluded that the waving lotion was not an irritant, but was capable of inducing sensitization (Table 9).[152]

In a similar study (same procedure), the skin irritation and sensitization potentials of an acid wave product containing 22.6% Glyceryl Thioglycolate (pH 6.9–7.2) were evaluated using the repeated insult patch test. The product was applied at a concentration of 33.0% (effective concentration of Glyceryl Thioglycolate 7.5%) to 53 subjects (17–73 years old). Skin reaction patterns indicative of sensitization and/or cumulative irritation were observed in 27 subjects (Table 9).[153]

In three additional studies, human subjects were patch tested with a commercial wave containing 22.0% Glyceryl Thioglycolate according to the same procedure. The products are identified as commercial waves 1, 2, and 3. Prior to testing, the products were diluted to a concentration of 33.0%. The results of these studies are summarized in Table 9.

The modified Draize-Shelanski-Jordan patch test was used to evaluate the skin irritation and sensitization potentials of Glyceryl Thioglycolate (2% in petrolatum). A total of 51 subjects (23–68 years old) were tested. Initially, the test substance was applied for 48 h to the back of each subject via an occlusive patch. The test substance was then applied (24 h contact period) on alternate days for a total of ten applications. Sites were graded at the end of each 24 h period. After a 13 day nontreatment period, a challenge patch was applied for 48 h to the back of each subject. A second challenge patch was applied (48 h contact period) 7 days later. Challenge sites were graded 48 and 72 h after application. Reactions ranging from mild erythema to intense erythema with edema were observed in 28 subjects: 15 subjects (induction and challenge phases), 9 subjects (induction only), and 4 subjects (challenge only). The test substance was an irritant when applied under occlusive patches (Table 9).[154]

In another study (same procedure), the skin irritation and sensitization potentials of 4% Glyceryl Thioglycolate (in petrolatum) were evaluated using 52 subjects (23–68 years old). Reactions ranging from mild erythema to intense erythema with edema were observed in 16 subjects (induction and challenge phases) and in 8 subjects (induction only). Reactions ranging from mild erythema to intense erythema were observed in 3 subjects (challenge only). The test substance was an irritant when tested under occlusive patches (Table 9).[155]

Skin irritation was also observed in 31 of 53 subjects (23–68 years old) tested (same procedure) with 2% aqueous Glyceryl Thioglycolate. Eleven subjects had reactions

ranging from mild erythema to intense erythema with edema during the induction phase and reactions ranging from mild erythema to intense erythema with edema and vesicles during the challenge phase. Additionally, 8 and 12 subjects had rections ranging from mild erythema to intense erythema with edema only during induction and challenge phases, respectively. The test substance was an irritant when tested under occlusive patches (Table 9).[156]

In another study (same procedure), skin irritation was observed in 37 of 51 subjects (23–68 years old) tested with 4% aqueous Glyceryl Thioglycolate. Reactions ranging from mild erythema to intense erythema with edema and vesicles were observed in 16 subjects (induction and challenge phases). Eleven subjects had reactions ranging from mild erythema to intense erythema with edema only during the induction phase. Ten subjects had reactions ranging from mild erythema to intense erythema only during the challenge phase. The test substance was an irritant when tested under occlusive patches (Table 9).[157]

In the preceding four studies, Glyceryl Thioglycolate was tested at concentrations of 2.0% in petrolatum (51 subjects), 2.0% in water (53 subjects), 4.0% in petrolatum (52 subjects), and 4.0% in water (40 subjects), respectively. It is important to note that of the total (4 groups) number of participants, 38 subjects were tested with all four solutions, 14 were tested with three solutions, and 1 was tested with two solutions.

Skin Sensitization

Ammonium Thioglycolate

The sensitization potential of Ammonium Thioglycolate was evaluated in 19 subjects with hand dermatitis (18–28 years old) using both open and closed patch tests. A group of 20 subjects served as the control. The concentrations of Ammonium Thioglycolate tested ranged from 0.3% to 7.0%. In open patch tests, positive reactions were noted only at concentrations ranging from 3.0 to 7.0%: 1 subject (3.0% Ammonium Thioglycolate), 1 subject (5.0% Ammonium Thioglycolate), and 2 subjects (7.0% Ammonium Thioglycolate). In closed patch tests, most of the positive rections were observed in individuals tested with concentrations ranging from 3.0 to 7.0%: 5 subjects (3.0% Ammonium Thioglycolate), 5 subjects (5.0% Ammonium Thioglycolate), and 8 subjects (7.0% Ammonium Thioglycolate). In the control group, 4 and 5 subjects had positive reactions to 5.0 and 7.0% Ammonium Thioglycolate, respectively (Table 9).[73]

Four hairdressers (19–20 years old) with eczematous dermatitis were patch tested (open patches) with a cold permanent waving lotion containing 5.0% Ammonium Thioglycolate. All had positive reactions to the lotion. Reactions persisted for more than 96 h. The 4 subjects were later patch tested with solutions containing 2.0% and 5.0% Ammonium Thioglycolate. Both solutions induced positive reactions that persisted for more than 96 h. Results were negative when 18 healthy subjects and 2 hairdressers without dermatitis were patch tested (open patches) with 5.0% Ammonium Thioglycolate solution (Table 9).[158]

Eight hairdressers (average age 31) and 4 clients (average age 57) were patch tested with 2.5% Ammonium Thioglycolate in petrolatum. All were patients dermatitis. A Finn chamber was applied to each subject and removed 48 h later. Sites were graded 30 min and 7 days after removal. Only reactions observed in a subject during both grading sessions were considered positive. One subject (hairdresser) had a positive reaction to the test substance (Table 9).[145]

The sensitization potential of Ammonium Thioglycolate in 85 patients was evaluated using the epicutaneous test. Sixty-eight patients who had become sensitized to Thioglycolic Acid hydrazide were tested with 0.5% and 1.0% Ammonium Thioglycolate. Seventeen patients, sensitive to Thioglycolic Acid glycolester, were tested with 1.0% and 2.0% Ammonium Thioglycolate. Positive reactions to 0.5% and 1.0% Ammonium Thioglycolate were observed in 24 of the 68 patients. Five of the 17 patients had positive reactions to 1.0% and 2.0% Ammonium Thioglycolate (Table 9).[105]

The sensitization potential of an aqueous solution of 1.25% Thioglycolic Acid (adjusted to pH 9.0–9.3 with ammonia) was evaluated using 20 subjects. Patches made of cotton were moistened with 0.5 ml of the test solution and applied (under coverlets) to the upper arm on Monday, Wednesday, and Friday for 3 consecutive weeks, and each patch remained for 24 h. Approximately 10 days after application of the last induction patch, challenge patches were applied to the original site and to a new site (adjacent to original site). Challenge patches were removed after 24 h, and reactions were scored at 48 and 96 h. Sensitization reactions were not observed in any of the subjects (Table 9).[114]

Glyceryl Thioglycolate

Four-hundred three patients with cosmetic-related dermatitis were patch tested with 2.5% Glyceryl Thioglycolate over a period of 64 months (1977–1983). Patch tests were applied to the upper back of each patient and removed after 48 h. In most patients, sites were graded 48, 72, 96, and 120 h after patch application. Allergic sensitization reactions were observed in 25 subjects (Table 9).[159]

In another study, 66 patients (16–65 years old) were patch tested with 2.5% Glyceryl Thioglycolate in petrolatum over a period of 8 years. All of the patients were employed as hairdressers. Glyceryl Thioglycolate induced allergic reactions in 6 subjects (Table 9).[160]

During a 3 month period, 7 hairdressers with dermatitis (on hands) were patch tested with 2.5% Glyceryl Thioglycolate in petrolatum. Five subjects developed allergic contact dermatitis. Allergic reactions were not observed in 47 control subjects (Table 9).[161]

OCCUPATIONAL EXPOSURE

Allergic contact dermatitis was observed in a hairdresser (21 years old) who had given cold permanent waves and shampoo treatments to 5 to 10 customers daily for approximately 7 months. During month eight, the hairdresser was patch tested (open patches) with seven different cold wave solutions containing Ammonium Thioglycolate and 0.3, 0.5, 0.7, 1, 3, 5, and 7% aqueous Ammonium Thioglycolate. Moderately strong positive reactions to all seven wave solutions were observed 24, 48, and 72 h after application. Erythema and swelling were observed 6 h after application of 7 and 5% Ammonium Thioglycolate and 24 h after application of 3% Ammonium Thioglycolate. All positive reactions persisted for more than 1 week. In order to confirm these results, patch tests (open patches) were conducted with 11 different cold permanent wave solutions containing Ammonium Thioglycolate. Open patch tests were also conducted with two shampoos, two hair rinses, and four hair treatments, all

of which had been used previously by the hairdresser. Moderately strong reactions to all cold wave solutions were noted 48 and 72 h after application. Reactions to the shampoos, hair rinses, and hair treatments were not observed. It was concluded that allergic reactions observed in the hairdresser were due to Ammonium Thioglycolate.[162]

Seven beauticians (16–20 years old) with hand dermatitis were patch tested (open patches) with an aqueous solution of 5% Ammonium Thioglycolate. Allergic reactions were observed in three subjects at 48 h postapplication.[163]

The sensitization potential of Ammonium Thioglycolate and Glyceryl Thioglycolate was evaluated using 11 (Group 1) and 6 (Group 2) female subjects (23–70 years old). Six of the 11 subjects (8 hairdressers, 3 clients) in Group 1 and 4 of 6 subjects (2 hairdressers, 4 clients) in Group 2 were atopic. The subjects in Group 1 were patch tested with the following: 1% Glyceryl Thioglycolate in petrolatum, 2.5% Ammonium Thioglycolate in petrolatum, and human hair samples that recently had been permed with a Glyceryl Thioglycolate permanent wave product. Hair samples, obtained from five beauty salon clients who were not in either experimental group, were collected immediately before and after application of the perm and at 2 weeks, 6 weeks, and 3 months postapplication. Prior to the study, the five beauty salon clients had not had their hair dyed, tinted, or permanent waved within the last year. The test substances were applied for 48 h to the upper back of each subject via Finn chambers secured with porous tape. Sites were scored 30 min and 7 days after chamber removal. Reactions were classified as positive only when observed on day 7. The 6 subjects in Group 2 were patch tested with 1% Glyceryl Thioglycolate in petrolatum, 2.5% Ammonium Thioglycolate in petrolatum, and human hair tresses (not samples from beauty shop clients) that had been permed with a Glyceryl Thioglycolate permanent wave product. Prior to testing, the tresses had never been permanent waved, dyed, or otherwise color treated. In Group 1, 11 subjects and 1 subject had positive reactions to 1% Glyceryl Thioglycolate and 2.5% Ammonium Thioglycolate in petrolatum, respectively. Also, in Group 1 the incidence of positive reactions to permed hair samples was as follows: samples collected on the day of perm application (2 subjects), samples collected at 2 weeks (3 subjects), and samples collected at 6 weeks (3 subjects). In Group 2, 6 subjects and 1 subject had positive reactions to 1% Glyceryl Thioglycolate and 2.5% Ammonium Thioglycolate, respectively. The incidence of positive reactions to permed tresses (human hair) in this group was as follows: freshly permed tresses (3 subjects), tresses 2 weeks after perm (3 subjects), and tresses 3 months after perm (2 subjects). None of the subjects, both groups included, had positive reactions to virgin hair, hair from beauty shop clients that had not been waved, or hair tresses that had not been permed. In another group of subjects (33 patients), the skin irritation potential of hair samples that had been waved with a Glyceryl Thioglycolate permanent wave product (same as previously stated) was evaluated. The hair samples tested were obtained from subjects 6 weeks after the perm had been applied. There was no evidence of skin irritation or sensitization in any of the subjects tested.[164]

In a recent publication, Ammonium Thioglycolate and Glyceryl Thioglycolate are referred to as a rare sensitizer and a common sensitizer, respectively, in both hairdressers and their clients. A new lightweight glove that protects workers against epoxy resin and acrylic compounds is being investigated for its use in protecting against Glyceryl Thioglycolate sensitization.[165]

SUMMARY

Ammonium Thioglycolate, Thioglycolic Acid, and Glyceryl Thioglycolate are used predominantly in permanent waving products. Use concentrations of these ingredients are as follows: Ammonium Thioglycolate (> 0.1–50.0%), Thioglycolic Acid (> 0.1–25.0%), and Glyceryl Thioglycolate (> 1.0– > 50.0%).

Noncosmetic uses of Thioglycolic Acid are as follows: raw material for the synthesis of thioglycolates and pharmaceuticals, vinyl stabilizer, and a reagent for iron.

Thirty to forty percent of a 25.0% solution (330 mg/kg) of ^{35}S-Thioglycolic Acid that was applied to dorsal skin of rabbits was excreted within 5 h.

After intravenous injection of ^{35}S-Sodium Thioglycolate (3 mg/kg) into a female monkey, the greatest counts of radioactivity were found in the kidneys, lungs, and spleen. In a similar study, radioactivity was greatest in the small intestine and kidneys of a rat that was injected intravenously with 50 mg/kg of ^{35}S-Thioglycolic Acid. Residual ^{35}S blood concentrations at 0.5 to 7 h postinjection did not exceed 5.3% in rats dosed with 100 mg/kg of ^{35}S-Thioglycolic Acid.

Most of the radioactivity was excreted in the urine in the form of neutral sulfate 24 h after 100 mg/kg of ^{35}S-Thioglycolic Acid was administered to groups of rats via intravenous and intraperitoneal injection. Similar results were noted after rabbits received 100 and 200 mg/kg doses of ^{35}S-Thioglycolic Acid. Significant concentrations of dithioglycolate were detected in the urine of rabbits 24 h after Thioglycolic Acid (100–150 mg/kg) was injected intraperitoneally. Negligible concentrations of Thioglycolic Acid were detected. After a 5.0% solution of Sodium Thioglycolate (70, 80, and 123 mg/kg doses) was injected intravenously into rabbits, the test substance was excreted mostly as inorganic sulfate and neutral sulfur. Small quantities of Thioglycolic Acid, as cysteine-thioglycolic acid mixed disulfide, have been identified in human urine.

The pulmonary excretion of hydrogen sulfide was not noted up to 10 h after intraperitoneal injection of a rat with 150 mg/kg of Sodium Thioglycolate.

None of the rats died after 1 h of exposure to an aerosol containing 60.0% Thioglycolic Acid.

Permanent wave formulations containing Ammonium Thioglycolate, concentrations up to 17.5%, were slightly toxic in acute oral toxicity studies involving rats. Similar results were reported for rats dosed with formulations containing Glyceryl Thioglycolate, concentrations up to 22.0%, and in a study in which rats were dosed with a 4% solution of Glyceryl Thioglycolate. In a subchronic study, no significant gross lesions were observed in rats that were injected intraperitoneally with 100 mg/kg of 5.0% Sodium Thioglycolate.

Both a permanent wave solution containing 10.98% Ammonium Thioglycolate and one containing 22% Glyceryl Thioglycolate were practically nontoxic in rabbits in acute dermal toxicity studies. In a 21 day dermal toxicity study, 1 of 12 rabbits died after receiving 0.75 ml/kg doses of a 17.5% Ammonium Thioglycolate cold wave product for 2 days and 2.0 ml/kg doses of the diluted product for 3 days. In another dermal toxicity study, none of the rabbits died after an acid wave product containing 22.6% Glyceryl Thioglycolate was applied 5 days per week for 4 weeks. Eleven of 18 animals given 4.0 ml/kg doses and 2 of 17 animals given 2.0 ml/kg doses of cold wave solutions containing 7.0% Ammonium Thioglycolate for 90 days died.

Transient conjunctival redness was observed in rabbits after the instillation of a cold

wave product containing 17.5% Ammonium Thioglycolate. Minimal ocular irritation also was observed in rabbits after instillation of a commercial acid wave containing 22.0% Glyceryl Thioglycolate. These were the highest concentrations of Ammonium and Glyceryl Thioglycolate tested.

Cold wave products containing 17.5% Ammonium Thioglycolate were classified as moderate skin irritants when applied to the skin (abraded and intact) of rabbits for 4 h (occlusive patches) and 24 h (semi-occlusive patches). A 7.0% Ammonium Thioglycolate solution also was classified as a skin irritant after being applied (cotton patches) for 24 h to abraded and intact skin of rabbits. Glyceryl Thioglycolate (100%) was classified as a severe skin irritant after being applied (occlusive patches) for 24 h to abraded and intact skin of rabbits. In similar studies, mild and severe skin irritation reactions were observed in rabbits after hair waving products containing 19.9 to 22.0% Glyceryl Thioglycolate were applied.

In open epicutaneous tests, repeated applications of 9% Thioglycolic Acid and 22% Glyceryl Thioglycolate induced skin irritation, but not sensitization, in guinea pigs. In other epicutaneous tests, mild sensitization reactions were observed in guinea pigs challenged with 30% Ammonium Thioglycolate. There were no reactions to 0.2% Ammonium Thioglycolate. Mild sensitization reactions to 5% Ammonium Thioglycolate, but not 1% Ammonium Thioglycolate, also were observed. Results from open epicutaneous tests also indicated that Glyceryl Thioglycolate was not a sensitizer in guinea pigs when tested at concentrations of 24% and 48%. In maximization tests, permanent wave products containing Ammonium Thioglycolate or dilutions of these products did not induce sensitization. Guinea pigs were challenged with Ammonium Thioglycolate concentrations that ranged from 0.5% to 7%.

Ammonium Thioglycolate, Thioglycolic Acid, Sodium Thioglycolate, and Glyceryl Thioglycolate were not mutagenic in the Ames test when tested with and without metabolic activation. In the sex-linked recessive lethal mutations test, Thioglycolic Acid and Sodium Thioglycolate were not mutagenic. Sodium Thioglycolate also was not mutagenic when evaluated in the micronucleus test. There was no evidence of carcinogenicity in mice or rabbits that received dermal applications of 1.0% Sodium Thioglycolate (in acetone) twice per week throughout the study. Mice were allowed to die spontaneously; rabbits were killed during the 85th week of treatment.

A single application of a 1.0 N Ammonium Thioglycolate (approximately 11.0% Thioglycolate) solution induced skin irritation in 3 of 39 patients, whereas 1.0% Ammonium Thioglycolate induced skin irritation in all of the 14 patients tested. Single applications of 6.5% and 7.0% Ammonium Thioglycolate and repeated applications of 6.5% Ammonium Thioglycolate did not induce skin irritation in normal subjects. However, repeated applications of permanent wave solutions containing 7.1% Ammonium Thioglycolate caused strong skin irritation reactions in normal subjects.

A lotion base containing 4.5% Thioglycolic Acid did not induce skin irritation in any of the patients tested.

A 2.0% aqueous solution of Glyceryl Thioglycolate was classified as a skin irritant after repeated applications were made to normal subjects. However, repeated applications of a permanent wave solution containing 14 to 15.4% Glyceryl Thioglycolate did not induce skin irritation in normal subjects.

Ammonium Thioglycolate (6.0%) was classified as a skin irritant and sensitizer after single applications (via elastopatches) were made to patients during induction and challenge. When repeated applications of 18.0% Ammonium Thioglycolate were

made to two groups of normal subjects (different experimental procedures), mild to moderate skin irritation was observed. In one of the two groups, probable allergic contact dermatitis was observed in 1 subject. Repeated applications of 14.4% Ammonium Thioglycolate did not induce clinically meaningful irritation or any evidence of induced allergic contact dermatitis in normal human subjects. In other repeated insult patch tests, a cold wave product containing 9.0% Ammonium Thioglycolate and a permanent wave solution containing 12.0% Ammonium Thioglycolate (diluted to 0.12% Ammonium Thioglycolate) did not induce skin irritation nor sensitization in normal subjects. However, in a similar test, mild to intense erythema (induction and challenge) was observed in normal subjects patch tested with a permanent wave solution containing 7.1% Ammonium Thioglycolate. Cold wave products containing 17.5% Ammonium Thioglycolate (diluted to 4.4% Ammonium Thioglycolate) were classified as either cumulative irritants or low-grade sensitizers in repeated insult patch tests involving normal subjects.

Skin sensitization, but not irritation, was observed in patients (hairdressers and clients) who received single applications of 0.25% to 2.5% Glyceryl Thioglycolate. In normal subjects, 2.0% and 4.0% concentrations of Glyceryl Thioglycolate induced skin irritation but not sensitization in repeated insult patch tests. Higher concentrations of Glyceryl Thioglycolate (20.1% and 20.2%) had the potential for inducing sensitization, but not irritation, when applied repeatedly to normal subjects. In other repeated insult patch tests, 10.8%, 18.0%, and 21.6% Glyceryl Thioglycolate did not induce clinically meaningful irritation nor any evidence of induced allergic contact dermatitis in normal subjects. However, repeated applications of 14.4% Glyceryl Thioglycolate did not induce irritant reactivity but did induce allergic contact dermatitis in 1 of 55 normal subjects. When repeated applications of 23.4% Glyceryl Thioglycolate were made to two groups of normal subjects (different experimental procedures), mild to moderate skin irritation was observed in one group, and mild to marked skin irritation was observed in the other group. In one of the two groups, 2 subjects had what was referred to as possible and probable moderate-grade allergic contact dermatitis.

In other studies (normal subjects), repeated insult patch tests were used to evaluate the skin irritation and sensitization potential of products containing Glyceryl Thioglycolate. Reactions ranging from no irritation or sensitization to intense erythema (induction and challenge) were observed in subjects patch tested with acid wave products containing 22.6% Glyceryl Thioglycolate. An acid permanent wave containing 15.76% Glyceryl Thioglycolate (diluted to 7.88% for challenge) was a skin irritant but not a sensitizer. When two acid wave products containing 22.6% Glyceryl Thioglycolate were tested, one of the products (diluted to 5.7% Glyceryl Thioglycolate) was a sensitizer but not an irritant. The other product (diluted to 7.5% Glyceryl Thioglycolate) induced reactions that were classified as sensitization and/or cumulative irritation.

Sensitization reactions were observed in patients patch tested (open and closed patches) with 3.0 to 7.0% Ammonium Thioglycolate. Additionally, sensitization reactions to 0.5 to 2.0% Ammonium Thioglycolate were observed in patients evaluated according to the epicutaneous test procedure. In normal subjects, 1.25% Ammonium Thioglycolate (cotton patches) and 5.0% Ammonium Thioglycolate (open patches) did not induce sensitization.

Glyceryl Thioglycolate induced sensitization in 25 of 403 patients patch tested. No allergic reactions were observed in patients patch tested with 2.5% Glyceryl Thiogly-

colate in petrolatum. Similar results were reported for 47 normal subjects patch tested with 2.5% Glyceryl Thioglycolate in petrolatum.

Sensitization reactions were observed in all 4 patients (hairdressers) patch tested (open patches) with a cold wave product containing 5.0% Ammonium Thioglycolate and with 2.0% and 5.0% Ammonium Thioglycolate. In another study, sensitization was observed in 1 of 12 patients (8 hairdressers, 4 clients) patch tested (Finn chambers) with 2.5% Ammonium Thioglycolate in petrolatum.

Glyceryl Thioglycolate (2.5% in petrolatum) induced allergic reactions in 6 of 66 patients (hairdressers) and 5 of 7 patients (hairdressers) patch tested. Sensitization reactions also were observed in all of the 11 patients (8 hairdressers, 3 clients) patch tested with 1.0% Glyceryl Thioglycolate in petrolatum.

DISCUSSION

Ammonium Thioglycolate and Thioglycolic Acid

In skin irritation studies involving normal subjects, Ammonium Thioglycolate was not an irritant at concentrations up to 7.0% when applied under cotton patches for 24 h.[95] In repeated insult patch tests (semi-occlusive patches), Ammonium Thioglycolate also did not appear to be an irritant or sensitizer at concentrations up to 14.4% when a total of nine induction patches was removed from each subject after 24 h of exposure, each followed by a 24 h nontreatment period prior to application of the next induction patch.[138,140] Ammonium Thioglycolate was a cumulative irritant and weak sensitizer when tested under occlusive conditions, with a 24 h nontreatment period between each induction exposure, at concentrations of 4.4% and 7.1%.[141,142]

Ammonium Thioglycolate elicited allergic reactions in patients patch tested at a concentration of 2.5% for 48 h. Most, if not all, of those who had positive reactions were hairdressers or clients.[145] One investigator reported that 18 of 19 patients who were hairdressers reacted positively when Ammonium Thioglycolate was tested under closed patches at concentrations ranging from 3.0 to 7.0%, but only 4 of 19 patients had positive responses when open patches were used.[73]

Ammonium Thioglycolate can be used safely by an individual at concentrations up to 14.4%, provided that use is infrequent. Clinical data indicate that the application of Ammonium Thioglycolate to clients by hairdressers has elicited allergic reactions in some of the hairdressers. This has been demonstrated in clinical studies involving a concentration of Ammonium Thioglycolate (2.5%) that is much lower than normal cosmetic use concentrations. Without adequate skin protection, repeated applications of cosmetic products containing Ammonium Thioglycolate by hairdressers to multiple clients over a period of time should be avoided.

Glyceryl Thioglycolate

Glyceryl Thioglycolate was not an irritant at concentrations of 14.0 to 15.4% in 100 normal subjects who received two 48 h patch applications separated by a 14 day nontreatment period. The results from human skin irritation and sensitization repeated insult patch tests using normal subjects vary according to the specific procedure used. In repeated insult patch tests, Glyceryl Thioglycolate was judged to be an irritant, but

not a sensitizer, when tested at a concentration of 22.6% under semi-occlusion. The test material remained in contact with the skin for 24 h, after which patches were removed and a 24 h nontreatment period preceded application of the next patch to the same test site.[138,140] An evaluation of other studies performed with occlusive patches according to the same procedure indicates that Glyceryl Thioglycolate was an irritant and a cumulative irritant and/or sensitizer at concentrations of 7.3 to 20.2%.[68,142,143,153]

Some investigators reported that Glyceryl Thioglycolate was a potential sensitizer, but not an irritant, in repeated insult patch tests, even though many of the induction application sites had to be changed because of irritation reactions.[149,152] One of these studies indicated that Glyceryl Thioglycolate was a potential sensitizer at a concentration of 5.7%. Repeated insult patch tests in which 2.0% and 4.0% concentrations were tested under occlusion indicated that Glyceryl Thioglycolate was an irritant but not a sensitizer.[157]

When Glyceryl Thioglycolate was tested at concentrations of 10.8, 14.4, 18.0, and 21.6% in an repeated insult patch test (semi-occlusive patches) in which the site was changed before each of the nine induction applications, separated by 24 h nontreatment period, Glyceryl Thioglycolate was neither an irritant nor a sensitizer.[138]

In clinical studies, mainly involving hairdressers, Glyceryl Thioglycolate elicited allergic reactions at concentrations down to and including 0.25%.[145,159–161]

Glyceryl Thioglycolate, like Ammonium Thioglycolate, appears to be safe for infrequent consumer use at concentrations of cosmetic use up to 15.4%. Clinical studies show that allergic reactions in hairdressers can be demonstrated at Glyceryl Thioglycolate concentrations of 0.25%. Without adequate skin protection, repeated applications of cosmetic products containing Glyceryl Thioglycolate by hairdressers to multiple clients over a period of time should be avoided.

CONCLUSION

Based on the available data included in this report, the Expert Panel concludes that hair products containing Ammonium Thioglycolate and Glyceryl Thioglycolate may be used safely, at infrequent intervals, at concentrations of Ammonium Thioglycolate and Glyceryl Thioglycolate up to 15.4% (as Thioglycolic Acid). Hairdressers should avoid skin contact and minimize consumer skin exposure.

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