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Final Amended Report on the Safety Assessment of Ammonium Thioglycolate, Butyl Thioglycolate, Calcium Thioglycolate, Ethanolamine Thioglycolate, Ethyl Thioglycolate, Glyceryl Thioglycolate, Isooctyl Thioglycolate, Isopropyl Thioglycolate, Magnesium Thioglycolate, Methyl Thioglycolate, Potassium Thioglycolate, Sodium Thioglycolate, and Thioglycolic Acid

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This safety assessment includes Ammonium and Glyceryl Thioglycolate and Thioglycolic Acid Butyl, Calcium, Ethanolamine, Ethyl, Isooctyl, Isopropyl, Magnesium, Methyl, Potassium, and Sodium Thioglycolate, as used in cosmetics. Thioglycolates penetrate skin and distribute to the kidneys, lungs, small intestine, and spleen; excretion is primarily in urine. Thioglycolates were slightly toxic in rat acute oral toxicity studies. Thioglycolates are minimal to severe ocular irritants. Thioglycolates can be skin irritants in animal and in vitro tests, and can be sensitizers. A no-observable-adverse-effect level for reproductive and developmental toxicity of 100 mg/kg per day was determined using rats. Thioglycolates were not mutagenic, and there was no evidence of carcinogenicity. Thioglycolates were skin irritants in some clinical tests. Clinically significant adverse reactions to these ingredients used in depilatories are not commonly seen, suggesting current products are formulated to be practically nonirritating under conditions of recommended use. Formulators should take steps necessary to assure that current practices are followed.

Keywords: ammonium thioglycolate; cosmetics; safety

Ethanolamine Thioglycolate was selected as a high priority cosmetic ingredient for review by the Cosmetic Ingredient Review (CIR) Expert Panel in 2002. Because safety test data on this thioglycolate salt may be relevant to the safety of other thioglycolate salts and esters and vice versa, the remaining cosmetic ingredients in this family listed in the *International Cosmetic Ingredient Dictionary and Handbook* have been included.[1] These are: Butyl Thioglycolate, Calcium Thioglycolate, Ethyl Thioglycolate, Isooctyl Thioglycolate, Isopropyl Thioglycolate, Magnesium Thioglycolate, Methyl Thioglycolate, Potassium Thioglycolate, and Sodium Thioglycolate.

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The CIR Expert Panel had completed a safety assessment of Ammonium Thioglycolate, Thioglycolic Acid, and Glyceryl Thioglycolate with the conclusion that these cosmetic ingredients may be safely used in hair care products at infrequent intervals, at concentrations not to exceed 15.4% (measured as Thioglycolic Acid); however, hairdressers should avoid skin contact and minimize consumer skin exposure.[2] Data from the earlier safety assessment of Ammonium Thioglycolate, Glyceryl Thioglycolate, and Thioglycolic Acid have been added to this report with the expectation that these data may be extended to the entire group of thioglycolate salts and esters.

Relevant to the ethanolamine moiety of Ethanolamine Thioglycolate, the CIR Expert Panel has completed a final report on the safety assessment of Triethanolamine (TEA), Diethanolamine (DEA), and Monoethanolamine (MEA). The Panel concluded at that time "TEA, DEA and MEA are safe for use in cosmetic formulation designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin."[3] In products intended for prolonged contact with the skin, the concentration of ethanolamines should not exceed 5%. MEA should be used only in 'rinse-off' products. TEA and DEA should not be used in products containing N-nitrosating agents."

In the United States, a group called the Thioesters Association has undertaken the development of additional safety test data, according to 2005 correspondence with E. Hunt of the organization. Those data that became available were included in this amended safety assessment.

CHEMISTRY

Definition and Structure

Table 1 summarizes the available chemical formulae and/or structural information on Thioglycolate Acid and its salts and esters, and lists the current definition of these ingredients as given in the *International Cosmetic Ingredient Dictionary and Handbook*.[1]

Chemical and Physical Properties and Reactivity

Available data describing the chemical and physical properties and reactivity of ingredients addressed in this safety assessment are given in Table 2.

Because the molecular weights (MW) of these Thioglycolic Acid derivatives vary considerably, a common practice is to express the concentration as equivalent levels of Thioglycolic Acid. Thus, a concentration of Ammonium Thioglycolate (MW 109.13) of 18% corresponds to a level of Thioglycolic Acid (MW 92.12) of 15.2% (18 × 92.12/109.13). A concentration of Glyceryl Thioglycolate (MW 166.15) of 23.4% corresponds to a level of Thioglycolic Acid of 13% (23.4 × 92.12/166.15).

Method of Manufacture

According to the Cosmetic, Toiletry, and Fragrance Association (CTFA), Thioglycolic Acid may be prepared via the reaction of sodium or potassium chloracetate with alkali metal hydrosulfide in aqueous medium.[4] The reaction mixture is acidified and purified by organic extraction and vacuum distillation.

Ammonium Thioglycolate may be prepared by mixing Thioglycolic Acid with aqueous ammonia.[4]

Glyceryl Thioglycolate is prepared via esterification of a mixture of glycerin and Thioglycolic Acid.[4] The result is a complex mixture of the α and β 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, according to a 1987 review letter by Redken Laboratories, Inc.

Sodium Thioglycolate is formed by reacting sodium sulfhydrate with sodium chloroacetate or electrolysis of dithioglycolic acid (from sodium sulfide and sodium chloroacetate).[5]

Information was not found on the manufacture of other Thioglycolic Acid salts and esters.

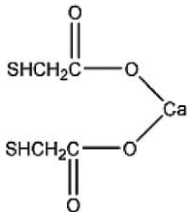
Analytical Methods

Thioglycolic Acid has been identified via the following methods: potentiometric titration with silver nitrate solution, thin-layer chromatography, high-pressure liquid chromatography, reversed-phase ion-pair high-performance liquid chromatography, gas chromatography, and high-performance liquid chromatography.[6-11]

Impurities

Cosmetic grade Ammonium Thioglycolate consists of Ammonium Thioglycolate (60%) and dithiodiglycolate (2% maximum).[5] Estrin et al[12] listed the

Table 1. Definitions and Synonyms for Thioglycolic Acid-Derived Cosmetic Ingredients

Ingredient and Formula	CAS No.	Definition	Synonym	Reference
Ammonium Thioglycolate $HSCH_2COONH_4$	5421-46-5	The ammonium salt of Thioglycolic Acid	Acetic Acid, Mercapto-, Monoammonium Salt Ammonium Mercaptoacetate Ammonium Thioglycollate Mercaptoacetic Acid, Monoammonium Salt Thioglycolic Acid Ammonium Salt	Gottschalck and McEwen,[1] 2006
Butyl Thioglycolate $HSCH_2COO(CH_2)_3CH_3$	10047-28-6	The ester of butyl alcohol and Thioglycolic Acid (q.v.)	Acetic Acid, Mercapto-, Butyl Ether Butyl Mercaptoacetate Butyl Thioglycollate Thioglycolic Acid, Butyl Ester	Gottschalck and McEwen,[1] 2006
Calcium Thioglycolate 	814-71-1	The calcium salt of Thioglycolic Acid	Acetic Acid, Mercapto-, Calcium Salt Calcium Mercaptoacetate Calcium Thioglycolate	Gottschalck and McEwen,[1] 2006
Ethanolamine Thioglycolate $HOCH_2CH_3NH_2 \cdot HOOCCH_2SH$	126-97-6	The salt of Thioglycolic Acid and ethanolamine	Acetic Acid, Mercapto-, Comp. with 2-Aminoethanol(1:1) Ethanolamine Thioglycollate Monoethanolamine Thioglycolate Mercaptoacetic Acid, Comp. with 2-Aminoethanol(1:1)	Gottschalck and McEwen,[1] 2006
Ethyl Thioglycolate $HSCH_2COOCH_2CH_3$	623-51-8	The ester of the ethyl alcohol and Thioglycolic Acid(q.v.)	Acetic Acid, Mercapto-, Ethyl Ester Ethyl Thioglycollate Ethyl mercaptoacetate (RIFM) Thioglycolic Acid, Ethyl Ester Ethyl-2-Mercaptoacetate Ethyl-α-Mercaptoacetate Ethyl Mercaptoacetic Acid Ethyl Ester Mercaptoacetic Acid	Gottschalck and McEwen,[1] 2006 Lewis,[176] 1993
Glyceryl Thioglycolate $HSCH_2COOCH_2CHOHCH_2OH$	30618-84-9	The monoester of glycerin and Thioglycolic Acid (q.v.)	Acetic Acid, Mercapto-, Monoester with 1,2,3-Propanetriol Glyceryl Monomercaptoacetate Glyceryl Monothioglycolate Glyceryl Thioglycollate Mercaptoacetic Acid, Monoester with 1,2,3-Propanetriol	Gottschalck and McEwen,[1] 2006

(continued)

Table 1. (continued)

Ingredient and Formula	CAS No.	Definition	Synonym	Reference
Isooctyl Thioglycolate $C_{10}H_{20}O_2S$	25103-09-7	The ester of Thioglycolic Acid and a mixture of branched chain octyl alcohols	Acetic Acid, Mercapto-, Isooctyl Ester Isooctyl Mercaptoacetate Isooctyl Thioglycollate Mercaptoacetic Acid, Isooctyl Ester Isooctyl Ester Mercaptoacetic Acid	Gottschalck and McEwen,[1] 2006 Lewis,[176] 1993
Isopropyl Thioglycolate $HSCH_2COOCH(CH_3)_2$	7383-61-1	The ester of isopropyl alcohol and Thioglycolic Acid (q.v.)	Acetic Acid, Mercapto-, Isopropyl Ester Isopropyl Mercaptoacetate Isopropyl Thioglycollate Thioglycolic Acid, Isopropyl Ester	Gottschalck and McEwen,[1] 2006
Magnesium Thioglycolate $(HSCH_2COO)_2Mg$	63592-16-5	The magnesium salt of Thioglycolic Acid	Acetic Acid, Mercapto-, Magnesium Salt Magnesium Mercaptoacetate Magnesium Thioglycollate Thioglycolic Acid, Magnesium Salt	Gottschalck and McEwen,[1] 2006
Methyl Thioglycolate $HSCH_2COOCH_2$	2365-48-2	The ester of methyl alcohol and Thioglycolic Acid (q.v.)	Acetic Acid, Mercapto-, Methyl Ester Methyl Mercaptoacetate Methyl Thioglycollate Thioglycolic Acid, Methyl Ester	Gottschalck and McEwen,[1] 2006
Potassium Thioglycolate $HSCH_2COOK$	34452-51-2	The potassium salt of Thioglycolic Acid	Acetic Acid, Mercapto-, Monopotassium Salt Mercaptoacetic Acid, Monopotassium Salt Potassium Mercaptoacetate Potassium Thioglycollate	Gottschalck and McEwen,[1] 2006
Sodium Thioglycolate $HSCH_2COONa$	367-51-1	The sodium salt of Thioglycolic Acid	Mercaptoacetic Acid, Sodium Salt Sodium 2-Mercaptethanoate Sodium Thioglycollate Sodium Mercaptoacetate Thioglycolic Acid, Sodium Salt	Gottschalck and McEwen,[1] 2006 Lewis,[176] 1993
Thioglycolic Acid $HSCH_2COOH$	68-11-1	An organic acid	Acetic\ Acid, Mercapto- Mercaptoacetic Acid Sulfhydrylacetic Acid Thioglycollic Acid Thiovanic Acid Glycolic Acid 2-Glycolic Acid Mercaptoacetate 2-Mercaptoacetic Acid α-Mercaptoacetic Acid 2-Thioglycolic Acid	Gottschalck and McEwen,[1] 2006 Lewis,[176] 1993

Table 2. Chemical and Physical Properties and Reactivity of Thioglycolic Acid-Derived Ingredients

Property	Description	Reference
	Ammonium Thioglycolate	
Molecular weight	109.13	Hampshire,[177] 2000a
Appearance	Pink liquid	Elder,[2] 1991
	Water white liquid	Hampshire,[177] 2000a
Odor	Repulsive odor	Hampshire,[177] 2000a
pH	5.5-6.8	Hampshire,[177] 2000a
Specific gravity	1.22 at 25°C	Hampshire,[177] 2000a
Boiling point	115°C	Hampshire,[177] 2000a
Freezing point	< –10°C	Hampshire,[177] 2000a
Miscibility/solubility	Miscible with water and ethanol; immiscible with acetone, benzene, chloroform, and ether	Elder,[2] 1991
UV spectra	$\lambda = 260$ nm	Elder,[2] 1991
Reactivity	Oxidizes in air to disulfide state	Elder,[2] 1991
	Incompatible with acid	Lewis,[176] 1984
	Butyl Thioglycolate	
Molecular weight	148.22	Lide,[179] 1993
Boiling point	85°C-88°C	Lide,[179] 1993
Density at 20°C	1.03	Lide,[179] 1993
	Calcium Thioglycolate	
Molecular weight	130.19	Budavari,[5] 1989
Form	White solid, trihydrate, prismatic rod crystals	Budavari,[5] 1989
Odor	Faint mercaptan	Budavari,[5] 1989
Melting point	Decomposes at 250°C	Budavari,[5] 1989; Lewis, 1993
Miscibility/solubility	Soluble in water, slightly soluble in alcohol, chloroform	Budavari,[5] 1989
	Ethanolamine Thioglycolate	
Molecular weight	153.2	Hampshire,[180] 2000b
Appearance	Water white to slightly pink	Hampshire,[180] 2000b
Odor	Slightly sulfide	Hampshire,[180] 2000b
pH	5.7-6.9	Hampshire,[180] 2000b
Specific gravity	1.187-1.198 at 25°C	Hampshire,[180] 2000b
Boiling point	110°C	Hampshire,[180] 2000b
Freezing point	< –10°C	Hampshire,[180] 2000b
	Ethyl Thioglycolate	
Molecular weight	120.18	Lewis,[176] 1984
Boiling point	156°C-158°C	Lewis, [176] 1984
Density at 15°C	1.0964	Lide,[179] 1993
Refractive index 20°C	1.4582	Lide,[179] 1993
Solubility	Alcohol and ether	Lide,[179] 1993
	Glyceryl Thioglycolate	
Molecular weight	166.2	Hampshire,[181] 2000c
Form	Water white, viscous liquid	Hampshire,[181] 2000c
Odor	Mild, characteristic sulfide	Hampshire,[181] 2000c
pH	2.0-3.5 (10% solution)	Hampshire,[181] 2000c
Boiling point	218°C	Hampshire,[181] 2000c
Freezing point	< –10°C	Hampshire,[181] 2000c
Specific gravity	1.300-1.320 at 25°C	Hampshire,[181] 2000c
Viscosity	≈250 cps at 25°C	Hampshire,[181] 2000c
Refractive index	1.4618 at 20°C	Elder,[2] 1991
Miscibility/solubility	Miscible with water	Elder,[2] 1991
UV spectra	$\lambda = 233.8$ nm	Elder,[2] 1991
Reactivity	Oxidizes in air	Elder,[2] 1991
	Isooctyl Thioglycolate	
Molecular weight	204.36	Lewis,[176] 1984
Appearance	Clear water white liquid	Lewis,[176] 1984
Odor	Fruity	Lewis,[176] 1984
Boiling point	125°C	Lewis,[176] 1984

(*continued*)

Table 2. (continued)

Property	Description	Reference
Refractive index	1.4606	Lewis,[28] 1997
Specific gravity	0.968-0.974 at 25°C	Hampshire,[182] 2000d
	Isopropyl Thioglycolate	
Molecular weight	134.19	Lide,[179] 1993
Boiling point	80°C-85°C	Lide,[179] 1993
Refractive index at 20°C	1.05	Lide,[179] 1993
	Methyl Thioglycolate	
Molecular weight	106.14	Lide,[179] 1993
Boiling point	42°C-43°C	Lide,[179] 1993
Refractive index	1.4657	Lide,[179] 1993
Solubility	Alcohol and ether	Lide,[179] 1993
	Sodium Thioglycolate	
Molecular weight	114.1	Budavari,[5] 1989; Lewis,[176] 1993
Form	Hygroscopic crystals	Budavari,[5] 1989; Lewis,[176] 1993
Odor	Characteristic	Budavari,[5] 1989; Lewis,[176] 1993
Miscibility/solubility	Soluble in water, slightly soluble in ethanol	Budavari,[5] 1989; Lewis,[176] 1993
Reactivity	Combustible; discolors on exposure to air or iron	Budavari,[5] 1989; Lewis,[176] 1993
	Thioglycolic Acid	
Molecular weight	92.12	Arkema,[29] 2005
Form	Colorless liquid	Arkema,[29] 2005
Odor	Pungent	Arkema,[29] 2005
Boiling point	120°C, 101.5°C	Lide,[179] 1993; Arkema,[29] 2005
Freezing point	–16.5°C	Arkema,[29] 2005
Viscosity	6.55 cP at 20°C	Arkema,[29] 2005
Specific gravity	1.325 g/cm^3 at 20°C	Arkema,[29] 2005
Miscibility/solubility	Miscible with acetone, ethanol, ethyl ether, other organic solvents and water; slightly soluble in chloroform	Lide,[179] 1993; Arkema,[29] 2005
Vapor pressure	10 mM Hg at 18°C	ACGIH,[134] 2002
n-Octanol/water partition coefficient	log $P_{OW} = 0.059$	Arkema,[29] 2005
Refractive index	1.5030 at 20°C	Arkema,[29] 2005
Reactivity	Combustible; readily oxidized by air; reacts with molecular oxygen to from Dithioglycolic Acid; reacts with diethyl acetylmalonate to form acetylmercatoacetic acid and diethyl malonate, reducing agent in conversion of Fe (III) to Fe (II)	Lewis,[176] 1993; Budavari,[5] 1989; Lienhard and Jencks,[183] 1965; Lee and Phil,[27] 1986

following in the Cosmetic, Toiletry, and Fragrance Association 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). The German cosmetics trade association reported Ammonium Thioglycolate is only producible as an aqueous solution with a maximal concentration of 71% (wt/wt).[13] Diammonium dithiodiglycolate and ammonium monochloroacetate impurities are <0.5% and <60 ppm, respectively.

Calcium Thioglycolate (trihydrate) is available in commercial and research grade with purity up to 99% with the following impurities: chloride, 0.05% maximum; sulfate, 0.005% maximum; Sr, 0.01% maximum; Na, 0.05% maximum; K, 0.005% maximum; Ba, Bi, Cd, Co, Cr, Cu, Fe, Li, Mn, Mo, Ni, Pb, or Zn, 0.0005% maximum.[14] Calcium Thioglycolate (trihydrate) with a purity of ≥99% (wt/wt) and with impurities dicalcium dithiodiglycolate and calcium dimonochloroacetate < 0.5% and < 50 ppm, respectively were reported.[13]

Ethanolamine Thioglycolate (as Monoethanolamine Thioglycolate) was also reported by the Industrieverband Körperpflege- und Waschmittel e.V. as only producible as an aqueous solution with a maximal concentration of 83% (wt/wt).[13] The impurities dimonoethanolamine dithiodiglycolate and monoethanolamine monochloroacetate are <0.5% and <0 ppm, respectively.

According to a 1987 review letter by Redken Laboratories, Inc, Cosmetic grade Glyceryl

Thioglycolate consists of Glyceryl Thioglycolate (80% ± 2%) and Thioglycolic Acid (2% maximum) as well as glycerin and traces of dithioglycolate species.[4]

CTFA (2006) reported data provided by 1 supplier of Potassium Thioglycolate in which several batches of this ingredient were analyzed using inductively coupled plasma mass spectrometry, with microwave detection. Impurity levels were reported as follows: As, Cd, Co, Cu, Ni, and Pb, <0.05 ppm; Cr and Mn, <0.10 ppm; and Zn, <0.3 ppm. Potassium Thioglycolate is only producible as an aqueous solution with a maximal concentration of 43% (wt/wt).[13] Dipotassium dithiodiglycolate and potassium monochloroacetate impurities are <0.5% and <30 ppm, respectively.

Sodium Thioglycolate is commercially available in research quantities with purities ranging from 98% to greater than 99.5% with the following impurities: sulfate, 0.005% maximum; K, 0.01% maximum; Ca and Mg, 0.005% maximum; Al, Ba, Bi, Cd, Co, Cr, Cu, Fe, Li, Mn, Mo, Ni, Pb, Sr, or Zn, 0.0005% maximum.[13] Sodium Thioglycolate can exist as an aqueous solution (46% wt/wt) and as a crystalline powder (98%), but the powder is not used in cosmetics.[13] Reported impurities are disodium dithiodiglycolate (<0.7%) and sodium monochloroacetate (<35 ppm).

Cosmetic grade Thioglycolic Acid consists of Thioglycolic Acid (78% minimum), iron (0.02 ppm maximum), and monochloroacetic acid (0.05% maximum).[4] 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).[12] IKW (2006) reported that Thioglycolic Acid was pure at ≥ 99%. Water content was <0.3% and dithiodiglycolic acid, thioglycolides, and monochloroacetic acid were reported as <0.4%, <0.3%, and <100 ppm, respectively.

USE

Cosmetic

According to the *International Cosmetic Ingredient Dictionary and Handbook*, these ingredients function in several different ways in certain limited cosmetic product categories as given in Table 3.[1]

Table 4 provides the information provided to the US Food and Drug Administration (FDA) by industry under a voluntary reporting program on the types of products in which these ingredients are used and the frequency of that use.[15] Data from a survey performed by the CTFA identified current use concentrations for ingredients as a function of product category are also given in Table 4.[16]

Thioglycolates reduce the cystine disulfide linkages in the hair cortex, thereby weakening the keratin molecule.[17,18]

Cold wave products containing Ammonium Thioglycolate may be expected to remain on the skin or hair for as long as 10 to 40 min.[19] Although permanent waves generally will process in 30 min, in actual practice, they may remain on the head for up to 1 h, according to Redken Laboratories, Inc's 1987 review letter. IKW described standard applications for depilatories, hair straighteners, and permanent waves as shown in Table 3.[13] Under conditions of actual usage, cold wave solutions containing Thioglycolates are not in intimate contact with nonhairy skin for any length of time.[20]

Permanent wave directions and literature include appropriate warnings, such as 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 permanent, if so), and checking the scalp for sensitivity or any evidence of sores, abrasions, or abnormal condition (if so, do not give permanent), reports Redken Laboratories, Inc's 1987 review letter.

Depilatory directions and literature also include warnings that direct product users not to exceed a total application time of 10 minutes; to use product externally only; to not use product on irritated, sun-burned, inflamed, or broken skin and skin around the eyes, nose, ears, nipples, perianal, and genitals; and before each use, test a small area on the skin where the hair is to be removed 24 hours prior to application to check for irritation or allergic reaction.[21] The directions warn that prolonged or frequent use of depilatory product may cause allergic reactions and failure to follow the directions and warnings may result in chemical burns.

As shown in Table 3, uses as hair dyes and colors have been reported for Ammonium Thioglycolate and Thioglycolic Acid. Hair dyes containing these ingredients as "coal tar" hair dye products are exempt

Table 3. Ingredients, Ingredient Functions, and Application as a Function of Cosmetic Product Category[1]

Cosmetic Product Category	Ingredient	Function	Applications
Depilatories	Calcium Thioglycolate	Depilating agent; exfoliant	In salts of Thioglycolic Acid, a dose of ~27 mg/cm^2 in emulsion is applied on the legs. Concentration corresponds to a max of 5% Thioglycolic Acid, pH = 12.5. Duration of 10 min is recommended. Frequency is every week.[15] Directions warn that prolonged or frequent use of depilatory products may cause allergic reactions and failure to follow the directions and warnings may result in chemical burns.[23]
	Potassium Thioglycolate	Depilating agent; hair-waving/straightening agent; reducing agent	
	Sodium Thioglycolate	Antioxidant; depilating agent; hair-waving/straightening agent; reducing agent	
	Thioglycolic Acid	Antioxidant; depilating agent; hair-waving/straightening agent; reducing agent	
Straighteners	Ammonium Thioglycolate	Hair waving/straightening agent; reducing agent	In salts of Thioglycolic Acid, a dose of ~20 mg/cm^2 in emulsion is applied to scalp after applying a 10-fold skin/hair partition factor. Concentration corresponds to a max. of 11% Thioglycolic Acid, pH = 9.5. Duration of application is 45 min, frequency is every 8 weeks.[15]
	Ethanolamine Thioglycolate	Depilating agent; hair-waving/straightening agent; reducing agent	
	Thioglycolate Acid	Antioxidant; depilating agent; hair-waving/straightening agent; reducing agent	
Permanent waves	Ammonium Thioglycolate	Hair waving/straightening agent; reducing agent	In salts of Thioglycolic Acid, a dose of ~20mg/cm^2 in watery solution is applied to scalp after applying a 10-fold skin/hair partition factor. Concentration corresponds to a max. of 11% Thioglycolic Acid, pH = 9.5. Duration of application is 30 min, frequency is every 8 weeks.[15]
	Ethanolamine Thioglycolate	Depilating agent; hair-waving/straightening agent; reducing agent	
	Glyceryl Thioglycolate	Hair-waving/straightening agent	
	Isooctyl Thioglycolate	Antioxidant; reducing agent	
	Thioglycolic Acid	Antioxidant; depilating agent; hair-waving/straightening agent; reducing agent	
Tonics, dressings, etc	Ammonium Thioglycolate	Hair waving/straightening agent; reducing agent	NA
Wave sets	Ammonium Thioglycolate	Hair waving/straightening agent; reducing agent	NA
Other noncoloring hair products	Ammonium Thioglycolate	Hair waving/straightening agent; reducing agent	NA
Dyes and colors	Ammonium Thioglycolate	Hair waving/straightening agent; reducing agent	NA
	Thioglycolic Acid	Antioxidant; depilating agent; hair-waving/straightening agent; reducing agent	

from the principal adulteration provision and from the color additive provisions §601 and §706 of the Federal Food, Drug, and Cosmetic Act of 1938 when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation.[22] The following caution statement should be displayed conspicuously on the labels of coal tar hair dyes:

> Caution—This product contains ingredients that may cause skin irritation on certain individuals, and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing eyelashes or eyebrows; to do so may cause blindness.

At its February 11, 1992, meeting, the CIR Expert Panel issued the following policy statement on coal tar hair dye product labeling:

> The CIR Expert Panel has reviewed the cosmetic industry's current coal tar hair dye product labeling,

Table 4. Cosmetic Ingredient Frequency of Use and Use Concentrations as a Function of Cosmetic Product Category

Product Category (Total Number of Products in Each Category[15])	2007 Uses[15]	2006 Use Concentrations[16] (%)
Ammonium Thioglycolate		
Noncoloring hair care products		
Straighteners (61)	7	8-19
Permanent waves (169)	43	7-19
Tonics, dressings, etc (623)	—	0.01
Wave sets (59)	7	—
Other (464)	1	—
Hair coloring products		
Dyes and colors (1600)	—	0.4
Total uses/ranges of Ammonium Thioglycolate	58	0.01-19
Calcium Thioglycolate		
Skin care products		
Depilatories (49)	10	5-7
Total uses/ranges for Calcium Thioglycolate	10	5-7
Ethanolamine Thioglycolate		
Noncoloring hair care products		
Straighteners (61)	1	12
Permanent waves (169)	2	9-17
Total uses/ranges for Ethanolamine Thioglycolate	3	9-17
Glyceryl Thioglycolate		
Noncoloring hair care products		
Permanent waves (169)	10	20
Total uses/ranges for Glyceryl Thioglycolate	10	20
Isooctyl Thioglycolate		
Noncoloring hair care products		
Permanent waves (169)	—	0.04
Total uses/ranges for Isooctyl Thioglycolate	—	0.04
Potassium Thioglycolate		
Skin care products		
Depilatories (49)	10	5-7
Total uses/ranges for Potassium Thioglycolate	10	5-7
Sodium Thioglycolate		
Skin care products		
Depilatories (49)	1	4
Total uses/ranges for Sodium Thioglycolate	1	4
Thioglycolic Acid		
Noncoloring hair care products		
Straighteners (61)	1	—
Permanent waves (169)	27	10-11
Hair coloring products		
Dyes and colors (1600)	31	0.3[a]
Skin care products		
Depilatories (49)	7	2-5
Total uses/ranges for Thioglycolic Acid	66	0.3-11

[a] 0.3% after dilution.

which recommends that an open patch test be applied and evaluated by the beautician and/or consumer for sensitization 24 hours after application of the test material and prior to the use of a hair dye formulation.

Since the recommendation on the industry's adopted labeling establishes a procedure for individual user safety testing, it is most important that the recommended procedure be consistent with current medical practice.

There is a general consensus among dermatologists that screening patients for sensitization (allergic contact dermatitis) should be conducted by the procedures used by the North American Contact

Table 5. Limitations/Warnings on Thioglycolic Acid and its Salts and Esters[184]

Ingredients	Allowed Field of Use/Product Categories/Use Level	Other Limitations and Requirements	Conditions of Use and Warnings
Thioglycolic Acid and its Salts	Other hair care products which are removed after application; Maximum allowed concentration: 2% ready for use, calculated as Thioglycolic Acid (pH 7 to 9.5)	—	Avoid contact with eyes. In the event of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear suitable gloves. Contains Thioglycolate. Follow the instructions. Keep out of reach of children.
Thioglycolic Acid and its Salts	Depilatories: 5% ready for use, calculated as Thioglycolic Acid (pH 7 to 12.7)	Avoid contact with eyes. In the event of contact with eyes, rinse immediately with plenty of water and seek medical advice.	Contains Thioglycolate. Follow the instructions. Keep out of reach of children.
Thioglycolic Acid and its Salts	Hair waving or straightening products for professional use; maximum allowed concentration: 11% ready for use, calculated as Thioglycolic Acid (pH 7 to 9.5)	—	Avoid contact with eyes. In the event of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear suitable gloves. Contains Thioglycolate. Follow the instructions. Keep out of reach of children. For professional use only.
Thioglycolic Acid and its Salts	Hair waving or straightening products for general use: 8% ready for use, calculated as Thioglycolic Acid (pH 7 to 9.5)	Avoid contact with eyes. In the event of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear suitable gloves.	Contains Thioglycolate. Follow the instructions. Keep out of reach of children.
Thioglycolic Acid Esters	Hair waving or straightening products for professional use: 11%, ready for use, calculated as Thioglycolic Acid (pH 6 to 9.5)	May cause sensitization in the event of skin contact. Avoid contact with eyes. In the event of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear suitable gloves.	Contains Thioglycolate. Follow the instructions. Keep out of reach of children. For professional use only.
Thioglycolic Acid Esters	Hair waving or straightening products for general use: 8%; pH 6 to 9.5	May cause sensitization in the event of skin contact. Avoid contact with eyes. In the event of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear suitable gloves.	Contains Thioglycolate. Follow the instructions. Keep out of reach of children.

Dermatitis Group and the International Contact Dermatitis Group.[137] Basically, these procedures state that the test material should be applied at an acceptable concentration to the patient, covered with an appropriate occlusive patch, and evaluated for sensitization 48 and 72 hours after application. The CIR Expert Panel has cited the results of studies conducted by both the North American Contact Dermatitis Group and the International Contact Dermatitis Group in its safety evaluation reports on cosmetic ingredients.

During the August 26-27, 1991 public meeting of the CIR Expert Panel, all members agreed that the cosmetic industry should change its recommendation for the evaluation of the open patch test from 24 hours to 48 hours after application of the test material.

The industry was advised of this recommendation and asked to provide any compelling reasons why this recommendation should not be made by the Expert Panel and adopted by the cosmetic industry. No opposition to this recommendation was received. At the February 11, 1992 public meeting of the CIR Expert Panel, this policy statement was adopted.

Glove Protection for Hairdressers

In the CIR Expert Panel original safety assessment of Ammonium Thioglycolate, Glyceryl Thioglycolate,

Table 6. Ammonium, Glyceryl, and Sodium Thioglycolate Acute Oral Toxicity

Test Substance	No. of Animals	Procedure	Results	Reference
		Ammonium Thioglycolate		
Cold wave (17.5% Ammonium Thioglycolate)	10 albino rats (208-260 g)	Oral dose	$LD_{50} > 1$ g/kg	Consumer Product Testing Company, Inc,[185] 1982b
Permanent waving solution (10.98% Ammonium Thioglycolate)	30 Sprague-Dawley rats (200-300 g)	Intubation	$LD_{50} = 1.8 \pm 0.2$ mL/kg	Applied Biological Sciences Laboratory, Inc,[186] 1982a
Permanent waving solution (7.1% Ammonium Thioglycolate)	30 Sprague-Dawley rats (200-300 g)	Intubation	$LD_{50} = 2.25 \pm 0.2$ mL/kg	Applied Biological Sciences Laboratory, Inc,[187] 1978a
Permanent waving solution (7% Ammonium Thioglycolate)	70 Sprague-Dawley rats (200-296 g)	Intubation	LD_{50} = between 3.0 and 3.5 g/kg	Bio-Technics Laboratories, Inc,[188] 1981a
		Glyceryl Thioglycolate		
Glyceryl Thioglycolate (75%)	60 Sprague-Dawley rats	Oral dose	$LD_{50} = 172$ mg/kg	Thioesters Association, 2006 (personal communication)
Glyceryl Thioglycolate (75%)	50 SPF-Wistar rats	Gavage	$LD_{50} = 172$ mg/kg	Thioesters Association, 2006 (personal communication)
Glyceryl Thioglycolate (67.9% in water)	30 Sprague-Dawley rats	Oral dose	NOAEL = 39 mg/kg	Thioesters Association, 2006 (personal communication)
Acid wave (22% Glyceryl Thioglycolate)	26 Crl: COBS albino rats (150-238 g)	Intubation	$LD_{50} = 1102 \pm 59.78$ mg/kg	Industrial Bio-Test Laboratories, Inc,[189] 1977a
Acid wave (19.9%-22.0% Glyceryl Thioglycolate)	10 albino rats (216-286 g)	Oral dose	$LD_{50} > 1$ g/kg	Consumer Product Testing Company, Inc,[190] 1982a
Exothermic acid wave (21% Glyceryl Thioglycolate)	10 Wistar albino rats (200-300 g)	Oral dose	$LD_{50} < 5$ g/kg	Consumer Product Testing Company, Inc,[191] 1982c
Glyceryl Thioglycolate (3.75% in water)	50 SPF-Wistar rats	Oral dose	$LD_{50} = 172$ mg/kg	Hoechst Aktiengeselischaft Pharma Forschung Toxikologie,[192] 1977
Glyceryl Thioglycolate (1% aqueous solution)	10 Sprague-Dawley rats	Intubation	$LD_{50} > 50$ mg/kg	Thioesters Association, 2006 (personal communication)
Glyceryl Thioglycolate	Groups of 4 rats (99-120 g)	Intubation	LD_{50} = between 0.1 and 0.5 mL/kg	UCLA,[193] 1976
		Sodium Thioglycolate		
Sodium Thioglycolate (5%)	10 CAF_1 mice (15-24 g)	Oral dose	$LD_{50} = 504 \pm 31$ mg/kg	Freeman et al,[60] 1956b

and Thioglycolic Acid, advice was given that hairdressers should avoid skin contact.[2] Traditionally, and as mandated in the European Union as shown in Table 5, gloves are worn to prevent these potentially irritating and sensitizing chemicals from damaging skin.

A study was conducted in which the effectiveness of various glove materials was determined.[23] ^{14}C-labeled Glyceryl Thioglycolate was mixed with 1.77 g of a commercially available Glyceryl Thioglycolate permanent wave solution (80% Glyceryl Thioglycolate, 2% Thioglycolic Acid, and 18% glycerine). To that mix was added 5.73 g of an aqueous solution containing 4% ammonium carbonate, 2% ammonium chloride, 1% disodium EDTA, 4.2% ammonium hydroxide, 0.2% hexadiethrine chloride, and 0.1% isoceteth 20. This mixture was calculated to have an equivalent level of Thioglycolic Acid of 11%. Immediately after this material was prepared, 250 μL was applied to the 1-cm^2 surface of glove material in a diffusion cell. Radiolabel appearing in the receptor solution (phosphate buffered saline, pH 7.4) was the measure of glove penetration. Glove materials evaluated were broadly grouped as polyvinylchloride (PVC), polyethylene, low-density polyethylene/ethylmethalate acrylate, vinyl, nitrile, latex, and latex/neoprene/nitrile blend. When determined at a fixed time of 2 hours, the permeation was least (0.14 $\pm$ 0.06 μg/cm^2) for the latex/neoprene/nitrile blend. In rank order, permeation through the rest of the materials was: latex glove material at 0.23 $\pm$ 0.09 μg/cm^2; polyethylene glove material at 0.56 $\pm$ 0.07 μg/cm^2; PVC glove material at 0.60 $\pm$ 0.25 μg/cm^2; nitrile glove material at 0.62 $\pm$ 0.20 μg/cm^2; low-density polyethylene and ethylmethalate acrylate glove material at 1.43 $\pm$ 0.09; and 2 different vinyl glove materials at 3.30 $\pm$ 0.54 and 13.7 $\pm$ 2.48 μg/cm^2. After 6 hours, the total permeation increased for all glove material, with latex increasing the least (<2-fold) and nitrile increasing the most (>300-fold). The authors did note that the glove materials become a reservoir for Glyceryl Thioglycolate, an issue if gloves are to be reused.

A second study included both glove material and/or human skin in vitro to determine the permeation of commercially obtained ^{14}C-Glyceryl Thioglycolate.[23] Again, using a diffusion cell mounted with either glove material alone (PVC, vinyl, nitrile, and latex), skin alone (rinsed at 10 minutes and unrinsed), or glove and skin, 250 μL of test material was applied to the 1-cm^2 surface of glove, skin, or the glove/skin combination mounted in a diffusion cell and appearance of radiolabel in either the skin or the receptor fluid was measured. Rinsing the skin sample with water at 10 minutes precluded any radiolabel either appearing in the skin or the receptor fluid. Likewise, the combination of any glove material and skin resulted in negligible radiolabel in the receptor fluid. The authors did suggest that, overall, latex was the most effective material and nitrile the least.

Regarding the use of latex gloves, in the 1980s, the FDA noted an increase in the number of deaths reportedly associated with sensitivity to natural latex proteins contained in medical devices. Scientific studies and case reports documented sensitivity to natural latex proteins found in a wide range of medical devices. To protect the public health and minimize the risks associated with the use of natural latex protein sensitivity, the FDA developed a labeling regulation that provides important information to individuals who are sensitive to natural latex proteins as follows: "Caution: This Product Contains Natural Rubber Latex Which May Cause Allergic Reactions." This rule was published in the Federal Register of September 30, 1997 (62 FR 51029). This rule was codified in Title 21 of the Code of Federal Regulations (21 CFR 801.437) and became effective on September 30, 1998.[24] This labeling regulation does not apply to nonmedical devices, including gloves that could be worn by hairdressers.

Thioglycolic Acid and its salts and esters are not included in the list of cosmetic ingredients that must not be used in cosmetic products that are marketed in Japan.[25] Thioglycolic Acid and its salts are permitted to be used in products considered to be quasi-drugs. Quasi-drugs are defined as "having a mild effect on the body, but are intended for neither the diagnosis, prevention, nor treatment of disease, nor to affect the structure or function of the body".[26]

Limitations on the use of Thioglycolic Acid and its salts and esters in cosmetic products that are marketed within the European Union are included in Table 5.

Noncosmetic

Thioglycolic Acid (mercaptoacetic acid) is used in the manufacture of pharmaceuticals and as a vinyl stabilizer and reagent for iron.[27,28] As a stabilizer for

vinyl chloride plastics, and when formed from the reaction of C10-16 alkyl mercaptoacetates with dichlorodioctylstannane and trichlorooctylstannane, Thioglycolic Acid is safe for use as an indirect food additive.[24] Thioglycolates reportedly are used in leather processing.[29]

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Absorption

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 hours and then fasted for 24 hours.[30] 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 hour, 5% to 8% of the dose of [^{35}S]Thioglycolic Acid applied had been excreted in the urine. The amount excreted at 5 hours 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 3 additional rabbits (same procedure). The authors concluded that the total amount absorbed over an extended period of time probably was related to the amount applied.

The absorption of Thioglycolic Acid as Ammonium Thioglycolate was studied in groups of Sprague-Dawley rats (5/sex; ~200 g).[13] A solution of [^{14}C]Thioglycolic Acid was neutralized with a 25% solution of ammonia resulting in 3 solutions of 11% Ammonium [^{14}C]Thioglycolate with pH 6, pH 7, and pH 8, respectively. Each exposure group of rats received approximately 300 mg of test material on the clipped dorsal skin for 30 minutes followed by a washing of the site. The test site was then neutralized with 0.3 mL of a "natural styling solution" containing 2.1% hydrogen peroxide for 10 minutes followed by a washing of the site. These applications were to mimic human exposure to hair waving products. After the second wash, the test sites were covered with 4 layers of gauze and the rats were placed into metabolism cages for 72 hours. Following the observation period, the animals were killed. The test sites and surrounding skin were excised and dissolved in Soluene-350 for radioactivity analysis. The radioactivity of the waste wash water, urine, and feces as well as the carcasses were also measured. Most of the radiolabel was removed from the rat skin during washing of the test material and neutralization solution (mean 96.1%-96.8%). The mean ^{14}C recovered in urine and feces in the pH 6, pH 7, and pH 8 exposure groups was 0.139%, 0.119%, and 0.137%, respectively. The mean ^{14}C content of the skin at the application site for the pH 6, pH 7, and pH 8 exposure groups was 0.82%, 0.57%, and 0.60%, respectively. The mean cutaneous absorption for 11% Ammonium [^{14}C]Thioglycolate for the pH 6, pH 7, and pH 8 exposure groups was 0.27%, 0.24%, and 0.26%, respectively. Cutaneous absorption and ^{14}C concentrations in urine, feces, and carcasses were higher in males than females, but it was determined that this was not statistically significant.[13]

A study of the protective abilities of glove materials also details the penetration potential of a permanent waves solution containing 11% Glyceryl Thioglycolate in human skin in vitro.[31] ^{14}C-labeled Glyceryl Thioglycolate (250 µL) was applied to a 1-cm^2 surface of skin mounted in a Franz-type diffusion cell in 12 replicates. Receptor fluid was measured for radiolabel at 0.5, 1, 1.5, 2, 4, 8, 24, 32, and 48 hours after application. The effectiveness of rinsing was also tested in this study, and 2 skin samples were rinsed at either 10 minutes or 1 hour after application with receptor medium and the rinsates measured for radiolabel. After 8 hours and no rinsing, the amount of [^{14}C] Glyceryl Thioglycolate that had permeated through the skin was 36.0 $\pm$ 9.1 µg/cm^2. At 48 hours, the amount with no rinsing was 10275 $\pm$ 1217 µg/cm^2. The amount of [^{14}C]Glyceryl Thioglycolate that permeated the skin in samples that had been rinsed 10 minutes after application was 0.20 $\pm$ 0.06 µg/cm^2 at 8 hours after application and 0.489 $\pm$ 0.15 µg/cm^2 at 48 hours after application. Rinsing the skin allowed for 99.96% of the dose to be recovered.

Distribution

The distribution of radioactivity in a female monkey (weight = 6 kg) was determined after intravenous (i.v.) injection of [^{35}S]Sodium Thioglycolate (3 mg/kg).[30]

Urine was collected up to 10 hours after injection, 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.[30]

The distribution of radioactivity in Holtzman rats (weights = 200-250 g) and in an adult New Zealand rabbit (weight not stated) after i.v. injection of [^{35}S]Thioglycolic Acid were investigated.[34] One rat was injected i.v. with 50 mg/kg of the test substance and killed 1 hour 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. The authors suggested that 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 6 rats injected i.v. with 100 mg/kg of the test substance and bled during periods of up to 7 hours. Residual ^{35}S blood concentrations during 0.5 to 7 hours after injection did not exceed 5.3% in any of the 6 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: α1-, α2-, β-, and γ-globulins and albumin. The test substance (70 mg/kg) was injected i.v. Most of the radioactivity was bound to albumin. The extent of this uptake amounted to 0.14% at 20 minutes after injection and had diminished to 0.016% at 3 hours. The small amount of radioactivity detected in albumin might have been due to isotopic exchange.

Metabolism

The metabolism and excretion of [^{35}S]Thioglycolic Acid was evaluated in male Holtzman rats (weight = 200-250 g) and in adult male New Zealand rabbits (weights not stated).[34] The test substance (100 mg/kg) was administered to 12 rats via i.v. injection and to 10 rats via intraperitoneal (i.p.) injection. Also, 2 rats were each given 75 mg/kg via i.p. injection. Animals injected i.v. (12 rats) comprised 1 group, and those injected i.p. (12 rats) comprised the other. Urine samples were collected 24 hours after injection, after which the administered ^{35}S was excreted, and excretion percentages were determined. The mean urine sulfate content for i.v. dosed rats was 82.3% ± 1.6% and for i.p. dosed rats was 90.6% ± 1.8%. Most of the radioactivity was excreted in the form of neutral sulfate. Two rabbits were injected i.p. with 100 mg/kg of the test substance, and 1 rabbit was injected i.p. with 200 mg/kg. Urine samples were collected 24 hours after injection. The mean urine sulfur content of the 3 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 7 rabbits via i.p. injection. Significant concentrations of dithioglycolate (average concentration 28%) were detected in the urine at 24 h after injection. Only negligible concentrations of Thioglycolate were detected.[32]

Excretion

The pulmonary excretion of Sodium Thioglycolate as hydrogen sulfide was investigated in the rat (weight and strain not stated).[30] The animal was injected i.p. with Sodium Thioglycolate 150 mg/kg. Expired air from the animal was analyzed for hydrogen sulfide over a period of 10 hours. Hydrogen sulfide was not detected in expired air at any time during the study. These authors also evaluated the urinary excretion of Sodium Thioglycolate using rabbits (weights and strain not stated). Four animals were injected i.v. 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 hours. 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. In a final study, these authors evaluated the urinary excretion of Sodium Thioglycolate in rats (weight and strain not stated) injected i.p. 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 hours. Quantities of inorganic sulfate excreted, expressed

Table 7. Ammonium Thioglycolate, Sodium Thioglycolate, and Thioglycolic Acid Acute Intraperitoneal and Intravenous Toxicity

Test Substance	Animals	Procedure	Results	Reference
		Ammonium Thioglycolate		
Ammonium Thioglycolate (53.6%)	5 cats	i.v. injection	LD_{50} = 175 mg/kg	Kensler and Elsner,[194] 1949
Ammonium Thioglycolate (53.6%)	12 rabbits	i.v. injection	LD_{50} = 100 mg/kg	Kensler and Elsner,[194] 1949
Ammonium Thioglycolate (53.6%)	22 Sherman rats	i.p. injection	LD_{50} = 165 ± 7 mg/kg	Kensler and Elsner,[194] 1949
Ammonium Thioglycolate (10.7%)	27 mice	i.p. injection	LD_{50} = 200 ± 13 mg/kg	Kensler and Elsner,[194] 1949
Ammonium Thioglycolate	Mice (20-25 g), no. not stated	i.p. injection	LD_{50} = 100-200 mg/kg	Doull et al,[195] 1962
		Sodium Thioglycolate		
Sodium Thioglycolate (5%)	10 CAF_1 mice (15-24 g)	i.p. injection	LD_{50} = 505 ± 57 mg/kg	Freeman et al,[60] 1956b
Sodium Thioglycolate (5%)	10 Osborne-Mendel rats (140-200 g)	i.p. injection	LD_{50} = 126 ± 9 mg/kg	Freeman et al,[60] 1956b
Sodium Thioglycolate	CF_1 mice, no. not stated	i.p. injection	LD_{50} = 200-300 mg/kg	Doull et al,[195] 1962
		Thioglycolic Acid		
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	Freeman et al,[60] 1956b
Thioglycolic Acid (5%)	1 monkey	i.v. injection; dose = 300 mg/kg	Death at 10 h after injection	Freeman et al,[60] 1956b
Thioglycolic Acid	ddy mice, no. not stated	i.p. injection	LD_{50} = 368-737 mg/kg	Shinoda et al,[196] 1974

as percentage (%) of administered radioactivity, ranged from 29% to 72%.

The urinary excretion of Ammonium and Sodium Thioglycolate mixtures was evaluated using rabbits (2.3-3.0 kg, strain not stated).[33] The lotions (L) tested were as follows: L-1 (0.6N Ammonium Thioglycolate, pH 9.3), L-5 (0.6N Ammonium Thioglycolate with 0.5% active benzalkonium chloride, pH 9.3), L-3 (0.6N Ammonium Thioglycolate with 0.5% sodium oleate, pH 9.3), L-7 (0.6N Ammonium Thioglycolate with 1.0% sodium salt of alkyl aryl polyether sulfonate, pH 8.6), L-14 (0.6N Ammonium Thioglycolate with 4.0% sodium salt of alkyl aryl polyether sulfonate), L-15 (0.6N Ammonium Thioglycolate with 4.0% benzalkonium chloride, pH 9.3), and L-19 (0.6N 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 were labeled with 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 hours 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).

Small quantities of Thioglycolic Acid, as cysteine-thioglycolic acid mixed disulfide, have been identified in human urine via high-voltage paper electrophoresis.[34]

Effect on Eating Behavior

A study was reported in which male Sprague-Dawley rats were fed a carbohydrate free, high-fat (HF) diet.[35] The rats were allowed 2 weeks to adapt to the diet while they were housed individually in a temperature-controlled colony room. The rats were then injected i.p. with a Thioglycolic Acid salt (single dose 200-1600 μmol/kg) to determine the effect on feeding. The particular Thioglycolic Acid salt used was not stated. The Thioglycolic Acid salt inhibited fatty acid oxidation decreasing the β-hydroxybutyrate

in the plasma, and was not associated with a decrease in circulating glucose in HF rats. The effect on food intake was tested in 2 different substrains (Zur:SD and Ico:OFA SD) of Sprague-Dawley rats. The threshold dose of the Thioglycolic Acid salt for eliciting eating was much higher in Zur:SD (between 800 and 1600 μmol/kg) in comparison with Ico:OFA SD rats (between 200 and 400 μmol/kg). The Thioglycolic Acid salt (400 μmol/kg) induced hyperglycemia in the Ico:OFA SD by increased glycogenolysis.

Male Sprague-Dawley rats were fed a HF or low-fat diet with or without the Thioglycolic Acid salt (800 μmol/kg).[36] The Thioglycolic Acid salt resulted in greater food intake in rats maintained on the HF diet. The Thioglycolic Acid salt enhanced the activity of both hepatic and celiac vagal afferent fibers, but there was not a significant difference between the 2 diets.

Effect on Keratin

Sodium Thioglycolate reduced the keratin framework of calluses.[37] Defatted calluses were placed in a Sodium Thioglycolate (0.5N, 5.7% in distilled water at pH 4.6) solution for 18 hours at 35°C. The keratin framework of the horny cells was loosened and an α-keratin pattern was observed.

Thioglycolic Acid could act to break the disulfide bond of cysteine in keratin.[38]

Calcium Thioglycolate (1%, 2%, and 4% wt/vol) was applied to the skin of male Wistar rats to see if the reduction of cysteine linkages, that weakens the keratin structure, increases the skin permeability of drugs.[39] Aminophylline, theophylline, and β-hydroxyethyltheophylline were applied to clipped skin that was pre-treated with or without Calcium Thioglycolate (10 mL 1, 2, 4 wt/vol%). Calcium Thioglycolate increased the rate of dermal absorption over that of polyoxyethylenelaurylether (BL-9EX) and dimethylsulfoxide (DMSO). The increase over controls (dermal drug alone) was 28.2 to 30.4 times. The increased permeability was not sustained for a long period of time after Calcium Thioglycolate was removed.

Miscellaneous Effects

The following effects of Thioglycolic Acid have been reported: potentiation of bradykinin-induced contractions of guinea pig gut and uterus; inactivation of hypocalcemic activity of the salivary gland hormone, β-parotin; stimulation of guinea pig skin histidase activity; inhibition of thyroid iodinating enzyme system (in calf thyroid) in the presence of a hydrogen peroxide-generating system; inhibition of uterine response to oxytocin in rats; diabetogenic effect in rats; reduction of rat hepatic succinoxidase activity; reduction of bovine antidiuretic factor activity; and inhibition of fatty acid oxidation.[40-54]

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Oral toxicity studies for Ammonium, Glyceryl, and Sodium Thioglycolate, tested alone and in formulations, using various rat strains and 1 mouse strain are summarized in Table 6. At the highest concentrations tested, the LD_{50} values for Ammonium (17.5%), Glyceryl (75%), and Sodium Thioglycolate (5%) were >1 g/kg, 0.172 g/kg, and 0.504 g/kg, respectively. In 1 study of Glyceryl Thioglycolate, a no-observable-adverse-effect level (NOAEL) of 39 mg/kg was reported.

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).[2] Animals were exposed to the aerosol for 1 hour and then observed for 14 days. Data on aerosol particle size were not provided. 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 hour after exposure. At necropsy, minor pulmonary abnormalities were observed.

Glyceryl Thioglycolate

The acute inhalation toxicity of an aerosol containing Glyceryl Thioglycolate was evaluated using a group of 5 male and 5 female Sprague-Dawley rats (control parameters and particle size not described, according to a 2005 communication with the Thioesters Association's E. Hunt). The rats were exposed to 2.04 mg/L for 1 hour in a 361-L chamber at a airflow of 75 L/min. After exposure, the animals were observed for 14 days. No deaths occurred during the observation period and no abnormalities were

observed at necropsy. The LC_{50} was greater than 2.04 mg/L.

Acute Intraperitoneal and Intravenous Toxicity

Acute i.p. and i.v. toxicity studies of Thioglycolic Acid and its ammonium and sodium salts are summarized in Table 7. Several different animal systems were used. For example, the LD_{50} in rats for 53.6% Ammonium Thioglycolate and 5% Sodium Thioglycolate were 165 mg/kg and 126 mg/kg, respectively. Thioglycolic Acid (5%) caused death in a monkey at a dose of 300 mg/kg.

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).[56] The solution was held in contact with the skin (clipped free of hair) of the trunk for 24 hours 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 $\pm$ 0.5 mL/kg.

Glyceryl Thioglycolate

The dermal toxicity of a commercial acid wave (pH 6.9-7.2) containing 22% Glyceryl Thioglycolate was evaluated using 8 New Zealand albino rabbits (weight 2.44-3.16 kg).[57] 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 skin of 2 animals in both dose groups was 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 hours after application, and animals were observed for 14 days. Two of the rabbits receiving the 4556 mg/kg dose died, and 1 rabbit died in the group receiving the 3038 mg/kg dose. The product was classified as practically nontoxic, and the dermal LD_{50} was between 3038 mg/kg and 4556 mg/kg.

The dermal toxicity of Glyceryl Thioglycolate was evaluated using 10 New Zealand white rabbits (5/sex).[55] The rabbits were treated with 200 mg/kg test material on a shaved area of the back (3 male rabbits and 2 female rabbits had abraded skin) for 24 hours. The rabbits were then observed for 14 days. No deaths or other toxicological findings were observed. The dermal LD_{50} was >200 mg/kg.

Sodium Thioglycolate

In the dermal absorption study discussed earlier, a solution of [^{35}S]Thioglycolic Acid (330 mg/kg) was applied to clipped skin of the backs of rats via inunction.[30] Animals receiving the 660 mg/kg dose died (cause of death not stated) within 24 hours, whereas none of the animals in the 330 mg/kg dose group died.

Short-Term Oral Toxicity

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.[58]

Short-Term Dermal Toxicity

Ammonium Thioglycolate

The dermal toxicity of 16 lotions containing 0.6N Ammonium Thioglycolate and 1 lotion containing 0.6N Sodium Thioglycolate using groups of male and female rabbits (weights 2.3-3.0 kg, strain not stated) were evaluated.[33] All but 1 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} values were calculated. The LD_{50} (mg of Thioglycolic Acid/kg per 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 $\pm$ 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

Table 8. Ammonium Thioglycolate, Glyceryl Thioglycolate, and Calcium Thioglycolate Ocular Irritation Studies

Test Substance	No. of Animals/Test System	Procedure	Results	Reference
		Ammonium Thioglycolate		
Cold wave (17.5% Ammonium Thioglycolate)	9 New Zealand rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 7 after instillation	Transient ocular reactions	Consumer Product Testing Company, Inc,[197] 1982d
Permanent waving Solution (10.98% Ammonium Thioglycolate)	9 Albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 after instillation	Nonirritant	Applied Biological Laboratories, Inc,[198] 1982c
Permanent waving solution (8.3% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 7 after instillation	Moderate ocular irritant	Bio-Technics Laboratories, Inc,[199] 1986a
Permanent waving solution (7.2% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 7 after instillation	Moderate ocular irritant	Bio-Technics Laboratories, Inc,[200] 1986b
Permanent waving solution (7.1% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 7 after instillation	Nonirritant	Applied Biological Laboratories, Inc,[201] 1978b
Permanent waving lotion (7.0% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 after instillation	Borderline ocular irritant (unrinsed eyes); nonirritant (rinsed eyes)	Hill Top Testing Services, Inc,[202] 1977a
Permanent waving lotion (7.0% Ammonium Thioglycolate)	9 rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 after instillation	Minimal irritant (unrinsed eyes);nonirritant (rinsed eyes)	Micro-Bio Testing and Research Laboratories, Inc,[203] 1982a
Permanent waving lotion (7.0% Ammonium Thioglycolate)	9 rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 after instillation	Nonirritant	Micro-Bio Testing and Research Laboratories, Inc, [203] 1982a
Permanent waving lotion (7.0% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 after instillation	Ocular irritant	Bio-Technics Laboratories, Inc,[204] 1981
Permanent waving lotion (5.8% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 after instillation	Moderate ocular irritant	Bio-Technics Laboratories, Inc,[205] 1986c
Permanent waving solution (5.0% Ammonium Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 3 after instillation	Nonirritant	Bio-Technics Laboratories, Inc,[206] 1981
		Glyceryl Thioglycolate		
Acid wave (22% Glyceryl Thioglycolate)	9 New Zealand albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 7 after instillation	Minimal ocular irritant	Industrial Bio-Test Laboratories, Inc,[207] 1977c
Exothermic acid wave (21% Glyceryl Thioglycolate)	3 New Zealand rabbits	Reactions scored up to day 7 after instillation	Nonirritant	Consumer Product Testing Company, Inc,[208] 1982e

(*continued*)

Table 8. (continued)

Test Substance	No. of Animals/Test System	Procedure	Results	Reference
Glyceryl Thioglycolate (67.9%)	3 New Zealand white rabbits	Reactions scored up to day 3 after instillation	Slightly irritating	Thioesters Association, 2006 (personal communication)
Glyceryl Thioglycolate (conc. not stated)	6 New Zealand white rabbits	Reactions scored up to day 7 after instillation	Mildly irritating	Thioesters Association, 2006 (personal communication)
Waving lotion (conc. of Glyceryl Thioglycolate not stated)	9 albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 14 after instillation	Nonirritant (rinsed eyes); slight irritant (unrinsed eyes)	Applied Biological Laboratory, Inc,[209] 1977
Waving lotion (conc. of Glyceryl Thioglycolate not stated)	9 albino rabbits	Eyes of 3 animals rinsed. Reactions scored up to day 14 after instillation	Nonirritant	Bio-Technics Laboratories, Inc,[210] 1980a
		Calcium Thioglycolate		
Calcium Thioglycolate (10%)	In vitro EYETEX™ and Chinese hamster lung cell assay	Details not given	Maximal average total score (MAS) was 4.0/110 and the 24-h total score was 2.7/110 for the EYETEX™ assaylogEC_{50} = 2.19 for the Chinese hamster lung cell assay	Okumura et al,[211] 1999
Calcium Thioglycolate powder (100%)	In vitro EYETEX™	Details not given	MAS was 79.7/110 and the 24-h average score was 52.3/110, which is classified as a severe/extreme eye irritant	Matsukawa et al,[212] 1999

Thioglycolate and no wetting agent. An LD_{50} of 93.3 $\pm$ 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.

The dermal toxicity of a cold wave product (pH 7.3-7.6) containing 17.5% Ammonium Thioglycolate in a 21-day study using 3 groups of 12 New Zealand white rabbits (6 males, 6 females; weights 1.5-3.5 kg per group) was evaluated.[59] The 3 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 3 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 3 animals per group were abraded. Each site was covered with a patch made of gauze (1-2 layers) and an occlusive binder for 4 hours. Sites were then wiped clean, and irritation reactions were scored according to the Draize scale. 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 significantly decrease the extent of dermal irritation, so the study was ended after the first week. Only 1 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 6 of the 7 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.

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 1 rabbit from the untreated control group. Severe to complete hair loss at the application site was observed in all experimental animals after repeated exposures. Fissures were noted at the application sites of 3 animals. Results from microscopic examination of sections of skin and hematological evaluations of blood indicated no treatment-related effects.[60]

Subchronic Intraperitoneal Toxicity

Sodium Thioglycolate, 100 mg/kg of 5% solution, was administered to 5 fasted male rats (125 $\pm$ 32.1 g) of the Osborne-Mendel (Yale) strain via i.p. injection.[61] The untreated control group consisted of 5 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 16th 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.

Subchronic Dermal Toxicity

The dermal toxicity of cold wave solutions (pH 9.0-9.5) containing 7.0% Ammonium Thioglycolate was evaluated using albino rabbits.[62] 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). A mild dermatitis was observed at microscopic examinations of sections of skin from approximately 50 animals.

Chronic Toxicity

The National Toxicology Program (NTP) has completed a 2-week (topical application) study of Sodium Thioglycolate using rats (Fischer 344) and mice (B6C3F1) dosed at 0, 11.25, 22.5, 45, 90, or 180 mg/kg; and 0, 22.5, 45, 90, 180, or 360 mg/kg, respectively, but the NTP has not evaluated the findings or prepared a report; a 13-week version of the same study is listed on the NTP website, and likewise raw data are available, but no study has been prepared.[63]

Ocular Irritation

Ammonium Thioglycolate

Several studies using rabbits to assess the ocular irritation potential of Ammonium Thioglycolate in formulations are summarized in Table 8. Results ranged from nonirritant to moderate ocular irritation, but the severity of the ocular irritation does not appear to be concentration related.

Glyceryl Thioglycolate

Several studies using rabbits to assess the ocular irritation potential of Glyceryl Thioglycolate, alone and in formulations, are summarized in Table 8. Results ranged from nonirritant to mildly or slightly irritating.

Calcium Thioglycolate

Two in vitro studies reporting the effects of Calcium Thioglycolate are summarized in Table 8. In 1 of the studies, undiluted Calcium Thioglycolate was determined to be a severe/extreme ocular irritant.

Dermal Irritation

Dermal irritation studies are summarized in Table 9 and discussed below.

Ammonium Thioglycolate

The skin irritation potential of a permanent waving solution containing 7.1% Ammonium Thioglycolate and 1.2% ammonium hydroxide was evaluated using 6 albino rabbits.[64] The solution was applied to the trunk (shaved and abraded skin), and sites were covered with gauze patches for 24 hours. Reactions were scored at 24 and 72 hours after application 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.

The skin irritation potential of a cold wave product (pH 7.3-7.6) containing 17.5% Ammonium Thioglycolate was evaluated using 4 New Zealand white rabbits.[65] The product was applied via an occlusive patch for 4 hours to abraded and intact skin. Reactions were scored at 4, 24, and 72 hours after application 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 hours. Reactions observed at 72 hours were very slight erythema and edema. The product had the potential for inducing moderate skin irritation, and the primary irritation index (PII) was 2.30.[65] 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 hours. The PII was 2.45, and the product had the potential for inducing moderate skin irritation.

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 10).[66]

The acute dermal irritation potential of 71% Ammonium Thioglycolate was studied using 3 male New Zealand albino rabbits.[13] Because irritant effects were anticipated, a single animal was tested first before the other 2 animals were used. The moistened test material (0.5 g) was applied to the shaved, intact skin on 1 flank for 3 minutes and for 4 hours on the other flank in the first animal. The sites were semi-occluded. The test material was nonirritating in the first animal, so it was applied to a single flank in the other 2 animals for a duration of 4 hours (the other flank served as a control). The animals were examined for signs of erythema, eschar, and edema and skin reactions were measured 1, 24, 48, and 72 hours after termination of exposure. The undiluted test substance was determined to be slightly irritating to intact, shaved rabbit skin, but there was no evidence of corrosive effect on the skin.

Calcium Thioglycolate

The acute dermal irritation potential of 99.8% Calcium Thioglycolate (as Calcium Thioglycolate Trihydrate) was studied using 3 male New Zealand albino

Table 9. Animal Skin Irritation Studies

Test substance	No. of Animals/Test System	Procedure	Results	Reference
		Ammonium Thioglycolate		
Ammonium Thioglycolate (71%)	3 New Zealand albino rabbits	4 h application to intact skin (semiocclusive patches)	Slight irritant	IKW,[13] 2006
Hydrophilic ointments (0.05%-30% Ammonium Thioglycolate)	10 Hartley guinea pigs	Not stated	Nonirritant	Itoh et al,[65] 1985
Cold wave (17.5% Ammonium Thioglycolate)	4 New Zealand white rabbits	4 h application to abraded and intact skin (occlusive patches)	Moderate skin irritant	Consumer Product Testing Company, Inc,[64] 1982f
Cold wave (17.5% Ammonium Thioglycolate)	4 New Zealand white rabbits	24 h application to abraded and intact skin (semiocclusive patches)	Moderate skin irritant	Consumer Product Testing Company, Inc, [64] 1982f
Permanent waving lotion (10.98% Ammonium Thioglycolate)	6 rabbits (strain not stated)	24 h application to abraded and intact skin	Nonirritant	Applied Biological Sciences Laboratory, Inc,[213] 1982d
Permanent waving lotion (8.3% Ammonium Thioglycolate)	6 New Zealand rabbits	24 h application to abraded skin (gauze patches)	Moderate irritant	Bio-Technics Laboratories, Inc,[214] 1986d
Permanent waving solution (7.2% Ammonium Thioglycolate)	6 New Zealand rabbits	24 h application to abraded skin (gauze patches)	Primary dermal irritant	Bio-Technics Laboratories, Inc,[215] 1986e
Permanent waving solution (7.1% Ammonium Thioglycolate)	6 albino rabbits	24 h application to abraded and intact skin (gauze patches)	Nonirritant	Applied Biological Sciences Laboratory, Inc.,[63] 1974
Permanent waving solution (7.0% Ammonium Thioglycolate)	6 albino rabbits	24 h application to abraded and intact skin (gauze patches)	Corrosive material	Hill Top Testing Services, Inc,[216] 1977b
Permanent waving solution (7.0% Ammonium Thioglycolate)	6 rabbits (strain not stated)	24 h application to abraded and intact skin	Nonirritant	Micro-Bio Testing and Research Laboratories, Inc,[217] 1982b
Permanent waving solution (7.0% Ammonium Thioglycolate)	6 New Zealand rabbits	24 h application to abraded and intact skin	Slight irritant	Bio-Technics Laboratories, Inc,[218] 1981d
Ammonium thioglycolate (4%-7% solutions)	Rabbits (no. and strain not stated)	1 h application	Nonirritant	Cappel and Cappel,[94] 1946
Ammonium Thioglycolate (7.0%)	Rabbits (no. and strain not stated)	24 h application to abraded and intact skin (cotton patches)	Skin irritant	Cappel and Cappel,[94] 1946
Ammonium Thioglycolate (6.5%)	Rabbits (no. and strain not stated)	24 h application to abraded and intact skin (cotton patches)	Skin irritant (abraded skin)-Non-irritant (intact skin)	Cappel and Cappel, [94] 1946
Permanent waving solution (5.8% Ammonium Thioglycolate)	6 New Zealand rabbits	24 h application to abraded and intact skin (gauze patches)	Severe irritant	Bio-Technics Laboratories, Inc,[219] 1986f
Permanent waving solution (5.0% Ammonium Thioglycolate)	6 New Zealand rabbits	24 h application to abraded and intact skin (gauze patches)	Minimal irritant	Bio-Technics Laboratories, Inc,[220] 1981e
		Calcium Thioglycolate		
Calcium Thioglycolate (99.8%)	3 New Zealand albino rabbits	4 h application to intact skin (semiocclusive patches)	Moderate irritant	IKW,[13] 2006
		Ethanolamine Thioglycolate		
Ethanolamine Thioglycolate (83%)	3 New Zealand albino rabbits	4 h application to intact skin (semiocclusive patches)	Slight irritant	IKW,[13] 2006

(*continued*)

Table 9. (continued)

Test substance	No. of Animals/Test System	Procedure	Results	Reference
		Glyceryl Thioglycolate		
Glyceryl Thioglycolate (100%)	6 New Zealand white rabbits	24 h application to abraded and intact skin (occlusive patches)	Severe irritant	Food and Drug Research Laboratories, Inc,[67] 1980
Acid wave (22% Glyceryl Thioglycolate)	6 New Zealand albino rabbits	24 h application to abraded and intact skin (occlusive patches)	Mild irritant	Industrial Bio-Test Laboratories, Inc,[66] 1977d
Glyceryl Thioglycolate (67.9%)	3 New Zealand white rabbits	4 h application to intact skin (semioclusive patches)	Nonirritant	Thioesters Association, 2006 (personal communication)
Exothermic acid wave (21% Glyceryl Thioglycolate)	6 New Zealand white rabbits	24 h application to abraded and intact skin (occlusive patches)	Severe irritant	Consumer Product Testing Company, Inc,[221] 1982g
Commercial wave product (19.9%-22% Glyceryl Thioglycolate)	6 New Zealand white rabbits	2 h application to abraded and intact skin (occlusive patches)	Mild irritant	Consumer Product Testing Company, Inc,[222] 1982h
		Potassium Thioglycolate		
Potassium Thioglycolate (43%)	3 New Zealand albino rabbits	4 h application to intact skin (semioclusive patches)	Slight irritant	IKW,[13] 2006
		Sodium Thioglycolate		
Sodium Thioglycolate (98%)	3 New Zealand albino rabbits	4 h application to intact skin (semioclusive patches)	Moderate irritant	IKW,[13] 2006
		Thioglycolic Acid		
Thioglycolic Acid (99%)	EpiDerm Skin Model	3 min and 1 h application to EpiDerm tissues	Corrosive	IKW,[13] 2006

Table 10. Animal Skin Sensitization Studies

Test Substance	Concentration	Animals	Procedure	Results	Reference
		Ammonium Thioglycolate			
10.98% Ammonium Thioglycolate (in permanent waving solution)	0.5% Ammonium Thioglycolate (induction and challenge)	10 Hartley albino guinea pigs	Maximization test	No sensitization	Applied Biological Sciences Laboratory, Inc,[75] 1982e
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	Bio-Technics Laboratories, Inc,[77] 1986g
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	Bio-Technics Laboratories, Inc,[78] 1986h
7% Ammonium Thioglycolate (in permanent waving solution	0.35% Ammonium Thioglycolate (induction), 7% Ammonium Thioglycolate (challenge)	10 Hartley guinea pigs	Maximization test	No sensitization	Micro-Bio Testing & Research Laboratories,[76] 1982c
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	Bio-Technics Laboratories, Inc,[74] 1981f
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	Bio-Technics Laboratories, Inc,[73] 1986i
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	Bio-Technics Laboratories, Inc,[72] 1980b
Ammonium Thioglycolate	30% (induction), 0.2%-30% (challenge)	8 guinea pigs	Closed epicutaneous test	Mild sensitization	Itoh et al,[65] 1985
Ammonium Thioglycolate	10% (induction), 1%-5% (challenge)	20 white guinea pigs	Epicutaneous test	Weak sensitization	Schulz,[71] 1973
Ammonium Thioglycolate	50% in pet. (induction and challenge)	33 Dunkin-Hartley albino guinea pigs	Buehler method	No sensitization	IKW,[13] 2006
Ammonium Thioglycolate	0.5%, 8.0%, and 20% (active material) in acetone/water/olive oil (2:2:1 vol/vol)	20 CBA/Ca/Ola/Hsd mice	Local lymph node assay	Sensitization, EC_3 = 0.65%	IKW,[13] 2006
		Calcium Thioglycolate			
Calcium Thioglycolate	2.5%, 5.0%, 10%, and 30% (wt/vol) in propylene glycol	20 CBA/Ca/Ola/Hsd mice	Local lymph node assay	Sensitization at 30%	IKW,[13] 2006

(continued)

Table 10. (continued)

Test Substance	Concentration	Animals	Procedure	Results	Reference
		Ethanolamine Thioglycolate			
Ethanolamine Thioglycolate (83%)	0.25%, 0.5%, 1.0%, 2.5%, 5.0%, 10%, and 25% (wt/vol) in propylene glycol	40 CBA/Ca/Ola/Hsd mice	Local lymph node assay	Sensitization at 25%	IKW,[13] 2006
		Glyceryl Thioglycolate			
Glyceryl Thioglycolate (80%)	As is	10 Hartley guinea pigs	3, 6 h exposures (induction); 24 h challenge after 2 weeks nontreatment period	No sensitization	Leberco Testing, Inc,[80] 1984
Glyceryl Thioglycolate (80%)	48%	6 guinea pigs	Open epicutaneous test	No sensitization	Maibach,[79] 1979
Glyceryl Thioglycolate (80%)	24%	8 guinea pigs	Open epicutaneous test	No sensitization	Maibach,[79] 1979
Glyceryl Thioglycolate (67.9%)	10% (in NaCl and Freund; induction), 67.9% (induction), 67.9% (challenge)	30 Dunkin-Hartley guinea pigs	Maximization test	Very weak sensitization	Thioesters Association, 2006 (personal communication)
Glyceryl Thioglycolate	1% and 10% (in distilled water; induction), 5% and 10% (in distilled water; challenge)	30 Dunkin-Hartley guinea pigs	Maximization test	Sensitization	Thioesters Association, 2006 (personal communication)
		Potassium Thioglycolate			
Potassium Thioglycolate (43%)	0.25%, 0.5%, 1.0%, 2.5%, 5.0%, 10%, 25%, and 50% in propylene glycol	40 CBA/Ca/Ola/Hsd mice	Local lymph node assay	Sensitization at $\geq$25%	IKW,[13] 2006
		Sodium Thioglycolate			
Sodium Thioglycolate (98%)	0.25%, 0.5%, 1.0%, 2.5%, 5.0%, and 10% in propylene glycol	32 CBA/Ca/Ola/Hsd mice	Local lymph node assay	Sensitization at 10%	IKW,[13] 2006
		Thioglycolic Acid			
Thioglycolic Acid (1.25% aqueous)	1.25% Thioglycolic Acid (induction), 2.5% Thioglycolic Acid (challenge)	10 Hartley or Connaught guinea pigs	10 intradermal injections (induction). Animals challenged 10-14 days after induction period	No sensitization	Voss,[81] 1958

rabbits.[13] Because irritant effects were anticipated, a single animal was tested first before the other 2 animals were used. The moistened test material (0.5 g) was applied to the shaved, intact skin on 1 flank for 3 minutes and for 4 hours on the other flank in the first animal. The sites were semi-occluded. The test material was nonirritating in the first animal, so it was applied to a single flank in the other 2 animals for a duration of 4 hours (the other flank served as a control). The animals were examined for signs of erythema, eschar, and edema and skin reactions were measured 1, 24, 48, and 72 hours after termination of exposure. The undiluted test substance was determined to be moderately irritating to intact, shaved rabbit skin, but there was no evidence of corrosive effect on the skin.

Ethanolamine Thioglycolate

The acute dermal irritation potential of 83% Ethanolamine Thioglycolate (as Monoethanolamine Thioglycolate) was studied using 3 male New Zealand albino rabbits.[13] Because irritant effects were anticipated, a single animal was tested first before the other 2 animals were used. The moistened test material (0.5 g) was applied to the shaved, intact skin on 1 flank for 3 minutes and for 4 hours on the other flank in the first animal. The sites were semi-occluded. The test material was nonirritating in the first animal, so it was applied to a single flank in the other 2 animals for a duration of 4 hours (the other flank served as a control). The animals were examined for signs of erythema, eschar, and edema and skin reactions were measured 1, 24, 48, and 72 hours after termination of exposure. The undiluted test substance was determined to be slightly irritating to intact, shaved rabbit skin, but there was no evidence of corrosive effect on the skin.

Glyceryl Thioglycolate

The skin irritation potential of a commercial acid wave (pH 6.9-7.2) containing 22% Glyceryl Thioglycolate was evaluated using 6 New Zealand albino rabbits.[67] The product was applied to 2 sites (1 intact, 1 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 hours 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 (maximum = 8), indicating that the product was mildly irritating to the skin of rabbits.

The skin irritation potential of undiluted Glyceryl Thioglycolate was evaluated using 6 New Zealand white rabbits (weights 2-4 kg).[68] The test substance was applied (0.5 mL, occlusive patches) for 24 hours 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 hours 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 hours after application. Severe and moderate edema (abraded and intact skin) was observed in all animals at 24 and 72 hours after application, respectively. It was concluded that Glyceryl Thioglycolate was extremely irritating to the skin of rabbits.

Potassium Thioglycolate

The acute dermal irritation potential of 43% Potassium Thioglycolate was studied using 3 male New Zealand albino rabbits.[13] Because irritant effects were anticipated, a single animal was tested first before the other 2 animals were used. The moistened test material (0.5 g) was applied to the shaved, intact skin on 1 flank for 3 minutes and for 4 hours on the other flank in the first animal. The sites were semi-occluded. The test material was nonirritating in the first animal, so it was applied to a single flank in the other 2 animals for a duration of 4 hours (the other flank served as a control). The animals were examined for signs of erythema, eschar, and edema and skin reactions were measured 1, 24, 48, and 72 hours after termination of exposure. The undiluted test substance was determined to be slightly irritating to intact, shaved rabbit skin, but there was no evidence of corrosive effect on the skin.

Sodium Thioglycolate

The acute dermal irritation potential of 98% pure Sodium Thioglycolate was studied using 3 male New

Zealand albino rabbits.[13] Because irritant effects were anticipated, a single animal was tested first before the other 2 animals were used. The moistened test material (0.5 g) was applied to the shaved, intact skin on 1 flank for 3 minutes and for 4 hours on the other flank in the first animal. The sites were semi-occluded. The test material was nonirritating in the first animal, so it was applied to a single flank in the other 2 animals for a duration of 4 hours (the other flank served as a control). The animals were examined for signs of erythema, eschar, and edema and skin reactions were measured 1, 24, 48, and 72 hours after termination of exposure. The undiluted test substance was determined to be moderately irritating to intact, shaved rabbit skin, but there was no evidence of corrosive effect on the skin or systemic toxicity.

Thioglycolic Acid

An acute dermal irritation study of 99% pure Thioglycolic Acid was reported.[13] Because of anticipated corrosivity, the study was performed using the in vitro EpiDerm Skin Model and not rabbit skin. Duplicate EpiDerm tissues were treated with 50 µL of 99% pure Thioglycolic Acid for a duration of 3 minutes or 1 hour. The tissues were incubated at 37°C in a humidified atmosphere of 5% CO_2 in air. Toxicity to the tissues was measured by the conversion of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) to formazan by viable cells in tissues treated with test material relative to the tissues treated with distilled water (negative control). The positive control was 8.0N potassium hydroxide. The mean viability was 4.96% after 3 minutes and 6.60% after 1 hour. Mean tissue viability values of less than 10% after 3 minutes are considered corrosive, thus it was concluded that 99% pure Thioglycolic Acid has the potential to be corrosive in vivo and should be classified as "causes severe burns."

Dermal 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.[69] 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-hour 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 hours 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 considered an irritant, but not a sensitizer.

Glyceryl Thioglycolate

The skin irritation and sensitization potentials of 22% Glyceryl Thioglycolate (pH 7.4) were evaluated using the open epicutaneous test.[70] 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-hour 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 hours 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.

A skin irritation and sensitization study of 80.31% Glyceryl Thioglycolate (22% vol/vol in water, pH 7.4) using 8 white spotted, Himalayan guinea pigs (weights 300-450 g) was reported.[71] 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 hours 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 hours 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.

Dermal Sensitization

Dermal sensitization studies are summarized in Table 10 and discussed below.

Ammonium Thioglycolate

The sensitization potential of Ammonium Thioglycolate was evaluated using the epicutaneous test.[72] 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 induced 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 3 guinea pigs. None of the guinea pigs had sensitization reactions to 2% or 1% Ammonium Thioglycolate. In a second experiment, 40 guinea pigs were induced with derivatives of Thioglycolic Acid (same procedure) and later challenged with 5% Ammonium Thioglycolate. Half of the animals were induced with 10% Thioglycolic Acid hydrazide, and the remaining half were induced with 10% Thioglycolic Acid glycolester. Weak sensitization reactions on challenge with 5% Ammonium Thioglycolate were observed only in 2 animals that had been sensitized to Thioglycolic Acid hydrazide.

The sensitization potential of a permanent waving solution containing 1.14% Ammonium Thioglycolate and 1.17% ammonium hydroxide was evaluated in a maximization test using 10 Hartley albino guinea pigs.[73] During the first induction, the solution, both undiluted and emulsified in Freund's complete adjuvant (FCA), 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.

Bio-Technics Laboratories, Inc used a maximization test to evaluate the sensitization potential of a permanent waving solution containing 5.8% Ammonium Thioglycolate and 1.28% ammonium hydroxide.[74] 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 FCA 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 hours 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.

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.[75]

The sensitization potential of another permanent waving solution (pH 7) containing 10.98% Ammonium Thioglycolate and 1.0% diammonium dithioglycolate was evaluated according to a modified maximization test.[76] The product was diluted with distilled water and FCA 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 after injection, the test substance was applied for 48 hours 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 hours to the flank (clipped free of hair) of each animal. Sites were scored 24 and 48 hours 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.

The sensitization potential of a permanent waving solution containing 7.0% Ammonium Thioglycolate, 5.0% urea, and 1.2% ammonium hydroxide was evaluated using a maximization test.[77] During the first phase of induction, 10 Hartley guinea pigs were given intradermal injections of the waving solution (concentration 5%). The effective concentration of

the test material was 0.35%. The solution was injected alone and in FCA. After a 7-day nontreatment period, the waving solution (full strength) was applied topically for 48 hours (second induction). The animals were challenged with a 24-hours 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).

The sensitization potential of Ammonium Thioglycolate was reported using the closed epicutaneous test.[65] 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 there were no reactions to 0.2% Ammonium Thioglycolate. It was concluded that Ammonium Thioglycolate was a mild sensitizer.

A maximization test was used to evaluate the skin sensitization potential of a permanent waving solution containing 8.3% Ammonium Thioglycolate and 1.40% ammonium hydroxide.[78] 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.

The sensitization potential of another permanent waving solution containing 7.2% Ammonium Thioglycolate and 1.5% ammonium hydroxide was evaluated 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.[79]

The sensitization potential of Ammonium Thioglycolate was studied using Dunkin-Hartley albino guinea pigs.[13] Twenty animals (10/sex) plus a control group of 10 animals (5/sex) were tested. An additional 3 guinea pigs were used to determine the minimum irritant and maximum nonirritant concentrations for the study. During the induction phase, 0.6 g of the test material at 50% concentration in white petrolatum (50% wt/wt) was applied to 1 side of the animals' trunks on days 0, 7, and 15. The vehicle was applied to the controls. Test sties were occluded for 6 hours. The challenge was performed 14 days later with the same formulation of test material and petrolatum on the untreated flank. The animals were examined 24 and 48 hours after the patch removal and responses were recorded. Some animals (number not stated) had intended irritation effects during the induction phase. Macroscopic examinations after the challenge phase showed evidence of delayed sensitivity in 1 guinea pig. No abnormalities were observed in the control animals. The authors concluded that the test material was not a dermal sensitizer. These authors also investigated the skin sensitization potential of Ammonium Thioglycolate using CBA/Ca/Ola/Hsd female mice in a local lymph node assay. There were 5 mice in each of the 3 dose groups and the control group. The mice received 25 μL of topical solution consisting of 0%, 0.5%, 8.0%, or 20.0% (active matter) of the test material in a mixture of acetone/water/olive oil (2:2:1 by vol) on the dorsal surface of each ear lobe once daily for 3 consecutive days. Five days after the first application of solution, all mice received radiolabeled thymidine (^{3}HTdR) by i.v. injection in the tail vein. All mice were killed 5 hours after the ^{3}HTdR injection. The lymph nodes of the mice were removed and studied for proliferation with ^{3}HTdR. The values were then used to calculate the stimulation index (SI). All mice in the 20.0% dose group died after the third application. The SI values for the 0.5% and 8.0% dose groups were 2.7 and 17.0, respectively. The EC_3 theoretical concentration was calculated as 0.65%. The study concluded that Ammonium Thioglycolate in acetone/water/olive oil was sensitizing in mice.

Calcium Thioglycolate

The skin sensitization potential of Calcium Thioglycolate (as Calcium Thioglycolate Trihydrate) in CBA/Ca/Ola/Hsd female mice was studied in a local lymph node assay.[13] There were 4 mice in each of 4 dose groups and the control group. The mice received 25 μL of topical solution consisting of 0%, 2.5%, 5.0%, 10.0%, and 30.0% (wt/vol) of the test material in propylene glycol on the dorsal surface of each ear lobe once daily for 3 consecutive days. Five days after the first application of solution, all mice received ^{3}HTdR by i.v. injection in the tail vein. All mice were killed 5 hours after the ^{3}HTdR injection. The lymph nodes of the mice were removed and studied for proliferation with ^{3}HTdR. The values were then used to calculate the SI. There were no signs of dermal irritation or systemic toxicity in any

of the dose groups. The SI values for the 2.5%, 5.0%, 10.0%, and 30.0% dose groups were 0.97, 1.19, 1.39, and 4.13, respectively. The EC_3 theoretical concentration was not calculated. The study concluded that Calcium Thioglycolate in propylene glycol was sensitizing in mice at 30% (wt/vol).

Ethanolamine Thioglycolate

The skin sensitization potential of 83% Ethanolamine Thioglycolate (as Monoethanolamine Thioglycolate) was investigated in CBA/Ca/Ola/Hsd female mice in a local lymph node assay.[13] A total of 8 dose groups and 2 control groups consisting of 4 mice each were used in this study (3 dose groups were originally used, but additional groups were added when the first groups did not elicit any systemic effects). The mice received 25 µL of topical solution consisting of 0%, 0.25%, 0.5%, 1.0%, 2.5%, 5.0%, 10.0%, or 25.0% (wt/vol) of the test material in propylene glycol on the dorsal surface of each ear lobe once daily for 3 consecutive days. Five days after the first application of solution, all mice received ^{3}HTdR by i.v. injection in the tail vein. All mice were killed 5 hours after the ^{3}HTdR injection. The lymph nodes of the mice were removed and studied for proliferation with ^{3}HTdR. The values were then used to calculate the SI. There were no signs of dermal irritation or systemic toxicity in any of the dose groups. The SI values for the 0.25%, 0.5%, 1.0%, 2.5%, 5.0%, 10.0%, and 25.0% dose groups were 1.63, 0.86, 1.18, 1.12, 0.93, 0.53, and 5.89, respectively. An additional test at 10% yielded an SI value of 2.39. The EC_3 theoretical concentration was not calculated. The study concluded that 83% pure Ethanolamine Thioglycolate (as Monoethanolamine Thioglycolate) in propylene glycol was sensitizing in mice at 25% (wt/vol).[13]

Glyceryl Thioglycolate

The sensitization potential of commercial 80% Glyceryl Thioglycolate (pH 2.3-3.3) was evaluated using the open epicutaneous test. Six guinea pigs were tested with a 60% concentration of the test substance (effective concentration of Glyceryl Thioglycolate 48%).[80] 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 2 groups tested.

The sensitization potential of 80.0% Glyceryl Thioglycolate was evaluated using 10 male Hartley guinea pigs (380-423 g).[81] 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 hours. This procedure was repeated (same site) once per week for 3 weeks. After a 2-week nontreatment period, challenge patches were applied using a Webril patch as described above. Patches remained in place for 24 hours, and sites were scored 24, 48, and 72 hours 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.

A guinea pig maximization test was performed to study the sensitization of Glyceryl Thioglycolate.[55] Thirty female albino Dunkin Hartley guinea pigs (including 10 control animals) were used. Animals in the intradermal induction phase received 1% vol/vol test material in distilled water. In the topical induction phase, animals were patched with 10% vol/vol test material in distilled water. The induction phase was 21 days in length (between the intradermal induction and the topical challenge). In the topical challenge, animals were patched with 10% and 5% vol/vol test material in distilled water. During the intradermal induction, very slight to severe erythema was noted in all treated animals at the 24-hour observation. Very slight erythema was observed in 13 animals at the 48-hour observation. Very slight erythema was noted in 5 and 1 control animals at the 24- and 48-hour observation, respectively. In the topical induction, very slight to well-defined erythema and very slight to slight edema were noted at test sites of all treated animals 1 hour after treatment. Very slight to well-defined erythema and incidents of very slight edema were observed in 15 treated animals 24 hours after treatment. During the 10% challenge, 2 animals died (1was killed on day 20 for a self-inflicted wound; the other died of unknown causes on day 24). Very slight to well-defined erythema and incidents of very slight to slight edema were noted at the challenge sites of 9 treated animals after 24 hours. These effects persisted in 8 of the animals after 48 hours and developed in 1 other animal.

Very slight erythema and/or very slight edema was observed in 2 treated animals after 72 hours. No signs of erythema or edema were noted in the control animals. Desquamation was noted in the challenge sites of 10 treated animals and 7 control animals at the 48- and/or 72-hour observation period. In the 5% topical challenge, very slight and/or very slight edema were noted at the challenge sites of 8 treated animals after 24 hours and 6 treated animals after 48 hours. No signs of erythema or edema were noted in the control animals. Desquamation was noted in the challenge sites of 7 treated animals and 3 control animals at the 48- and/or 72-hour observation period. The sensitization rate of Glyceryl Thioglycolate in this study was 56%.

A maximization test used to evaluate the sensitization potential of 67.9% Glyceryl Thioglycolate also was reported.[55] Thirty Dunkin Hartley guinea pigs (male and female, 10/sex in the treated group and 5/sex in the control group) were tested. During the first induction (starting on day 1), a 10% solution (0.1 mL) of the test substance in saline at 0.9% and FCA was injected intradermally. During the second induction (starting on day 8), the test substance (original form) was applied by cutaneous route. The animals were challenged after a period of 12 days without treatment with cutaneous applications (0.5 mL each) of the vehicle (left flank) and the test substance (original form, right flank) for 24 hours with an occlusive dressing. Sites were scored 24 and 48 hours after removal of the patch. No deaths occurred and no clinical signs were observed during the study. Well-defined erythema was observed on the right flank of 1 treated animal after 48 hours during the challenge phase. Very slight erythema was noted in 5 animals after 24 and 48 hours were considered inconclusive of sensitization. No reactions were observed in the control animals. It was concluded that the allergenicity level of Glyceryl Thioglycolate in this study was very weak.

Potassium Thioglycolate

The skin sensitization potential of 43% Potassium Thioglycolate in CBA/Ca/Ola/Hsd female mice in a local lymph node assay was reported.[13] A total of 8 dose groups and 2 control groups consisting of 4 mice each were used in this study (3 dose groups were originally used, but additional groups were added when the first groups did not elicit any systemic effects). The mice received 25 µL of topical solution consisting of 0%, 0.25%, 0.5%, 1.0%, 2.5%, 5.0%, 10.0%, 25.0%, or 50.0% (wt/vol) of the test material in propylene glycol on the dorsal surface of each ear lobe once daily for 3 consecutive days. Five days after the first application of solution, all mice received ^{3}HTdR by i.v. injection in the tail vein. All mice were killed 5 hours after the ^{3}HTdR injection. The lymph nodes of the mice were removed and studied for proliferation with ^{3}HTdR. The values were then used to calculate the SI. There were no signs of dermal irritation or systemic toxicity in any of the dose groups. The SI for the 0.25%, 0.5%, 1.0%, 2.5%, 5.0%, 10.0%, 25.0%, and 50.0% dose groups were 2.27, 1.94, 1.29, 1.07, 1.25, 1.58, 4.83, 12.04, respectively. The EC_3 theoretical concentration was not calculated. The study concluded that Potassium Thioglycolate in propylene glycol was sensitizing in mice at $\geq$25% (wt/vol).

Sodium Thioglycolate

The skin sensitization potential of 98% pure Sodium Thioglycolate was investigated in CBA/Ca/Ola/Hsd female mice in a local lymph node assay.[13] There were 4 mice in each of the 3 dose groups and the control group. An additional 3 dose groups and a control group were added to the study. The mice received 25 µL of topical solution consisting of 0%, 0.25%, 0.5%, 1.0%, 2.5%, 5.0%, or 10% (wt/vol) of the test material in propylene glycol on the dorsal surface of each ear lobe once daily for 3 consecutive days. Five days after the first application of solution, all mice received ^{3}HTdR by i.v. injection in the tail vein. All mice were killed 5 hours after the ^{3}HTdR injection. The lymph nodes of the mice were removed and studied for proliferation with ^{3}HTdR. The values were then used to calculate the SI. There were no signs of dermal irritation or systemic toxicity in any of the dose groups. The SI for the 0.25%, 0.5%, 1.0%, 2.5%, 5.0%, and 10% dose groups were 1.16, 2.05, 0.92, 1.17, 2.32, and 6.70, respectively. The EC_3 theoretical concentration was not calculated. The study concluded that 98% pure Sodium Thioglycolate in propylene glycol was sensitizing in mice at 10% (wt/vol).

Thioglycolic Acid

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).[82] The

solution was injected intradermally (shaved skin on 1 side) into each animal 3 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 10th injection, the animals were challenged (new test sites) with 0.05 mL of 2.5% Thioglycolic Acid. Four Hartley and 5 Connaught guinea pigs served as untreated controls. Sensitization reactions were not observed in any of the animals.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

New Zealand white rabbits were topically exposed to Sodium Thioglycolate in vehicle (1:1 95% ethanol/distilled water) at doses of 10, 15, 25, and 65 mg/kg per day or vehicle alone from gestational day 6 through 29.[83] Twelve naturally mated females were assigned to each group in 2 replicate designs for a total of 24 animals per group. No maternal death was associated with the exposure. One female in the 25 mg/kg per day group delivered early. One doe in the 65 mg/kg per day group was removed due to a preexisting trichobezoar (hairball in stomach). Slight erythema appeared in a few females during the first 2 days of dosing at $\geq$15 mg/kg per day and progressed to include the 10 mg/kg per day dose after 4 days. Moderate to severe erythema and edema occurred at doses $\geq$15 mg/kg per day, and edema occurred in all dose groups by gestational day 16. Petechia at the dosing site and dry skin were noted in the high dose group at day 9 and in 1 rabbit in the 25 mg/kg per day dose group. There was a reduction in maternal body weight gain in certain groups; however, there were no consistent trends. Prenatal viability was unaffected by maternal exposure to Sodium Thioglycolate. The incidences of fetal external, visceral, and skeletal alterations were also unaffected. Body weights of male and female fetuses per litter and percentages of males and females per litter were equivalent for all dose groups. Developmental toxicity for rabbits under conditions of this study was determined to be $\geq$65 mg/kg per day.

NTP also reported a study in which pregnant Sprague-Dawley rats were topically exposed to Sodium Thioglycolate in vehicle (1:1 95% ethanol:-distilled water) at doses of 50, 100, and 200 mg/kg per day or vehicle alone from gestational day 6 through 19.[82] Twenty-five females were assigned to each group and monitored at regular intervals throughout gestation for clinical signs of toxicity. Sodium Thioglycolate was associated with 1 maternal death at the 200 mg/kg per day. Feed consumption (g/kg per day) was significantly increased above controls at 50 and 100 mg/kg per day, but not at 200 mg/kg per day. Maternal water consumption was significantly increased at 200 mg/kg per day, but maternal body weights were significantly reduced at that dose. Prenatal viability was unaffected by maternal exposure to Sodium Thioglycolate. Body weights of male and female fetuses were significantly lower than controls in the highest exposure groups, with no other evidence of embryofetal toxicity or treatment-related teratogenicity. Under the conditions of this study and based on these results, a NOAEL of 100 mg/kg per day was determined in rats.

GENOTOXICITY

In vivo micronucleus testing of Thioglycolic Acid has been completed in the mouse, by oral and dermal routes of administration and no genotoxicity was found.[82]

Genotoxicity studies are summarized in Table 11 and discussed below.

Ammonium Thioglycolate

The mutagenicity of Ammonium Thioglycolate was evaluated using *Salmonella typhimurium* strains TA 1535, TA 1537, and TA 1538.[84] The concentrations that were tested ranged from 0.25 to 5.0 mg/plate in strain TA 1535 and TA 1538 cultures and from 0.5 to 5.0 mg/plate in strain TA 1537 cultures. Ammonium Thioglycolate was not mutagenic.

Thioglycolic Acid

The mutagenicity of Thioglycolic Acid was evaluated using *S. typhimurium* strains TA 1535, TA 1537, and TA 1538. Thioglycolic Acid (diluted with DMSO) was tested at concentrations of 1, 10, 100, and 1000 μg/plate with or without metabolic activation.[85] All concentrations were incubated with each bacterial strain for 48 hours (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

Table 11. Genotoxicity Studies

Test Substance	Concentration Tested	Strains Tested	Procedure	Results	Reference
		Ammonium Thioglycolate			
Ammonium Thioglycolate	0.25-5.0 mg/plate	*Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538	Ames test with and without metabolic activation	Not mutagenic	Zotos International, Inc,[83] 1987
		Thioglycolic Acid			
Thioglycolic Acid (in DMSO)	1 to 1000 μg/plate	*S. typhimurium* strains TA 1535, TA 1537, and TA 1538	Ames test with and without metabolic activation	Not mutagenic	Huntington Research Centre,[84] 1977
Thioglycolic Acid	Not stated	*Escherichia coli* strain Sd-4-73	Paper disk method	Not mutagenic	Iyer,[85] 1958
Thioglycolic Acid (in sucrose solution)	0.5%	Canton-S strain of *Drosophila melanogaster*	Sex-linked recessive lethal mutations test	Not mutagenic	Limbird,[86] 1971
		Glyceryl Thioglycolate			
Glyceryl Thioglycolate (80%)	25-1662 μg/plate	Human lymphocytes	Chromosomal aberration test, presence and absences of metabolic activation	Not clastogenic	Thioesters Association, 2006 (personal communication)
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	CTFA,[70] 1984
Glyceryl Thioglycolate	0.25-5.0 mg/plate	*S. typhimurium* strains TA 1535, TA 1537, TA 1538	Ames test with and without metabolic activation	Not mutagenic	Zotos International Inc.,[83] 1987
Glyceryl Thioglycolate	92.0-2946 μg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538	Ames test with and without metabolic activation	Not mutagenic	Thioesters Association, 2006 (personal communication)
		Sodium Thioglycolate			
Sodium Thioglycolate	Up to 3600 μg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538	Ames test with and without metabolic activation	Not mutagenic	Gocke et al,[90] 1981
Sodium Thioglycolate (in 5% saccharose)	25 mM	Berlin K and Basc strains of *Drosophila melanogaster*	Sex-linked recessive lethal mutations test	Not mutagenic	Gocke et al,[90] 1981
Sodium Thioglycolate	As is	3 mice (strain not stated)	Micronucleus test	Not mutagenic	Gocke et al,[90] 1981

controls. Thioglycolic Acid was not mutagenic with and without metabolic activation.

The mutagenicity of Thioglycolic Acid in strain Sd-4-73 of *Escherichia coli* was evaluated via the paper disk method.[86] 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.

A sex-linked recessive lethal mutation test was used in *Drosophila melanogaster* to evaluate the mutagenic potential of Thioglycolic Acid.[87] 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 for 24 hours 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.

Glyceryl Thioglycolate

The mutagenicity of 1% Glyceryl Thioglycolate (in DMSO) was reported (procedure not stated) using strains TA 1538, TA 98, TA 100, and TA 1537 of *S. typhimurium*.[88] The concentrations tested ranged from 0.02 to 1.50 mg/plate with and without metabolic activation. The test substance was not mutagenic.

The mutagenicity of Glyceryl Thioglycolate was evaluated in an Ames test using strains TA 1535, TA 1537, and TA 1538 of *S. typhimurium*.[83] The concentrations that were tested ranged from 0.25 to 5.0 mg/plate. Glyceryl Thioglycolate was not mutagenic.

An Ames test was used to study the mutagenicity of Glyceryl Thioglycolate using *S. typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100.[55] The test material was tested at concentrations equivalent to pure Glyceryl Thioglycolate ranging from 92.0 to 2946 μg/plate with and without metabolic activation by S9. The test material did not show mutagenic activity. The potential of 80% Glyceryl Thioglycolates to produce chromosomal aberrations was evaluated in a 2-part experiment using human lymphocytes. In the first experiment, the concentrations ranged from 103.9 to 1662 μg/mL and the cultured lymphocytes were treated for 4 hours in the presence of 2% S9 metabolic activation with cell harvest after a 20-hour expression period and for 4 hours without S9 with a 20-hour expression period. In the second experiment, the concentrations ranged from 25 to 400 μg/mL without metabolic activity and 103.9 to 1662 μg/mL with metabolic activity. For the second experiment, the lymphocytes treated with metabolic activation were exposed to 1% S9 for 4 h with a 20-hour expression period. The lymphocytes treated without metabolic activity were exposed to the test material for 24 hours. Negative and positive controls were employed in both parts of the experiment. The test substance was toxic, but did not induce any statistically significant increases in the frequency of chromosome aberrations in either part of the experiment, with or without metabolic activation. The negative and positive controls had results within the expected ranges. It was concluded that 80% Glyceryl Thioglycolate was nonclastogenic to human lymphocytes in vitro.

Sodium Thioglycolate

The mutagenic potential of Sodium Thioglycolate was evaluated using the micronucleus test.[89] Two doses of the test substance (285 mg/kg each) were administered i.p. to 3 mice at 0 and 24 hours. One animal served as the control. Bone marrow smears were prepared 30 hours after administration of the first dose. One thousand polychromatic erythrocytes per mouse were scored. The test substance was not mutagenic.

The mutagenic potential of Sodium Thioglycolate was evaluated using a sex-linked recessive lethal mutation test.[90] 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 3 successive broods. F2 progeny cultures with 2 or fewer wild-type males were routinely retested in the F3 generation to confirm X-linked recessive lethal mutations. The test substance was not mutagenic.

The mutagenic potential of Sodium Thioglycolate was evaluated in an Ames test.[91] Strains TA 1535, TA 100, TA 1538, TA 98, and TA 1537 of *S.*

typhimurium were each tested with at least 5 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.

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).[92] 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 the 49 mice and also 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. The authors concluded that Sodium Thioglycolate was not carcinogenic.

NEUROTOXICITY

Thioglycolates (No Specific Salt)

The effect of potassium bromate ($KBrO_3$) and Thioglycolate (salt not specified) on the auditory brainstem response in guinea pigs was evaluated.[93] Potassium bromate is used as a neutralizer for some permanents. Guinea pigs received a subcutaneous (s.c.) injection in the occipital region of saline (control), potassium bromate (50 mg/kg), or potassium bromate (50 mg/kg) with Thioglycolate (15 mg/kg) once every day for 2 weeks (n = 6 for each group). The potassium bromate with Thioglycolate treated guinea pigs had a significant decrease in body weight. Threshold hearing was significantly increased in the potassium bromate and potassium bromate with Thioglycolate treated guinea pigs. Auditory brain responses were affected by potassium bromate, with significantly prolonged wave I-II/I-III latency especially in combination with Thioglycolate. The IV-V interval, an index in the brainstem transmission, and nerve velocity were not altered by either treatment, indicating peripheral auditory perception is depressed, but central conduction is not affected by potassium bromate or exacerbated by Thioglycolate.

A study was conducted in which Hartley strain guinea pigs were injected subcutaneously in the occipital region with: (1) 20 or 50 mg/kg of potassium bromate alone, (2) 20 or 50 mg/kg of potassium bromate with 15 mg/kg Thioglycolate (which salt not specified), (3) 15 mg/kg Thioglycolate alone, or (4) saline alone for 14 consecutive days.[94] All adverse effects were seen in the potassium bromate alone and when combined with thioglycolate. The function of the vestibuloocular reflex system was studied using a caloric test coupled with electronystagmorphic recording. In the test, electrodes were attached to the canthi of both temporal orbits, and a reference electrode was attached to the vertex at the midline. The external ear was irrigated with ice water for 5 seconds and eye movement (nystagmus) was recorded. A balance test and histopathologic examinations were also completed. Vestibuloocular caloric hyperfunction, hyperactive vestibular response, sodium/potassium ATPase, and calcium ATPase activity was reduced in the bromate treated and enhanced with Thioglycolate. A loss of Purkinje cells and derangement of granule cell layer was also recorded. Thioglycolate alone caused no adverse response, although Thioglycolate increased the detrimental effects of potassium bromate.

CLINICAL ASSESSMENT OF SAFETY

Table 12 summarizes the dermal irritation and sensitization studies discussed below.

Dermal Irritation

Ammonium Thioglycolate

Skin irritation was not observed in subjects (number not stated) patch tested with 7.0% Ammonium

Table 12. Clinical Irritation and Sensitization Studies

Concentration	Procedure	Results	Reference
		Ammonium Thioglycolate	
7.0% (pH 9.6)	1-h application (number of subjects not stated)	Nonirritant	Cappel and Cappel,[94] 1946
7.0% (pH 9.6)	24-h application (number of subjects not stated)	Nonirritant	Cappel and Cappel,[94] 1946
6.5% (pH 9.4)	24-h application (number of subjects not stated)	Nonirritant	Cappel and Cappel,[94] 1946
6.5%	40-60-min applications daily for 2 months in 76 healthy individuals and 78 patients	No reactions	McNally and Scull,[57] 1948
0.5-1.5N(1.0N is ~11%)	48-h patch test in 39 patients	Erythema in 3 patients at 1.0 N and 6 patients at 1.5 N	Behrman et al,[95] 1949
4.61% Thioglycolic Acid + 0.86% ammonia	2-7-day patch test with challenge in 286 patients	No irritation or sensitization	Behrman et al,[95] 1949
4.61% Thioglycolic Acid + 0.86% ammonia	Patch test in 863 patients	Reactions in 16 subjects, 2 had definite positives at retest	Behrman et al,[95] 1949
≅ 6% (pH 9.3)	48-h induction/48 h challenge (using 0.55 N) in 223 patients	24 reactions at induction; 26 reactions at challenge	Downing,[101] 1951
1.25%	RIPT in 20 subjects	No sensitization reactions	Voss,[81] 1958
1%	Intradermal application in 14 patients	Irritation in all patients	Gelfand,[96] 1963
2.0% and 1%	Epicutaneous test in 17 patients	5 cases of sensitization	Schulz,[71] 1973
1% and 0.5%	Epicutaneous test in 68 patients	24 cases of sensitization	Schulz,[71] 1973
9% (pH 9.3-9.5)	RIPT in 52 subjects	No irritation or sensitization	Industrial Bio-Test Laboratories, Inc,[102] 1977e
4.4%	RIPT in 54 subjects	7 irritation reactions on induction and 3 reactions at challenge	Food and Drug Research Laboratories, Inc,[103] 1982b
4.4%	RIPT in 102 subjects	30 irritation reactions on induction and 2 reactions at challenge	Food and Drug Research Laboratories, Inc,[104] 1982c
0.12%	RIPT in 191 subjects	5 irritation reactions on induction and 7 reactions at challenge	UCLA,[105] 1983
7.1%	RIPT in 211 subjects	46 irritation reactions on induction and 22 reactions at challenge	UCLA,[106] 1984
0.3%-7%	Closed patch test in 19 patients	5 reactions at 3% and 5%, 8 at 7%	Itoh et al,[65] 1985
0.3%-7%	Open patch test in 19 patients	1 reaction to 3% and 5%, 2 at 7%	Itoh et al,[65] 1985
7.1%	21 patch application for 24 h in 25 subjects	irritation in all patients	UCLA,[97] 1985a
18%	RIPT in 205 subjects	irritation in 47% of subjects, no sensitization	Essex Testing Clinic, Inc,[107] 1990a
14.4%	RIPT in 220 subjects	12 irritation reactions on induction and 7 reactions at challenge	Essex Testing Clinic, Inc,[108] 1990b

(*continued*)

Table 12. (continued)

Concentration	Procedure	Results	Reference
		Glyceryl Thioglycolate	
22.6% (pH 6.9-7.2)	RIPT in 52 subjects	No irritation or sensitization	Industrial Bio-Test Laboratories, Inc,[109] 1977f
5.7%	RIPT in 52 subjects	19 reactions at induction and 12 at challenge (original site) and 8 at challenge (remote site)	Food and Drug Research Laboratories, Inc,[110] 1978
20.2%	RIPT in 30 subjects	6 reactions at induction and 1 at challenge (original site) and 1 at challenge (remote site)	Food and Drug Research Laboratories, Inc,[22] 1979
20.1%	RIPT in 29 subjects	6 reactions at induction and 7 at challenge (original site) and 3 at challenge (remote site)	Food and Drug Research Laboratories, Inc,[22] 1979
2% in petrolatum	RIPT in 51 subjects	9 reactions at induction and 15 at challenge (original site) and 4 at challenge (remote site)	UCLA,[111] 1981a
2% aqueous	RIPT in 53 subjects	8 reactions at induction and 11 at challenge (original site) and 12 at challenge (remote site)	UCLA,[112] 1981b
4% in petrolatum	RIPT in 52 subjects	8 reactions at induction and 16 at challenge (original site) and 3 at challenge (remote site)	UCLA,[113] 1981c
4% aqueous	RIPT in 51 subjects	11 reactions at induction and 16 at challenge (original site) and 10 at challenge (remote site)	UCLA,[114] 1981d
7.5% (pH 6.9-7.2)	RIPT in 53 subjects	Low-grade sensitization or cumulative irritation in 17 subjects, sensitization in 10	Food and Drug Research Laboratories, Inc,[115] 1982d
7.3%	RIPT in 51 subjects	Low-grade sensitization or cumulative irritation in 15 subjects, sensitization in 6	Food and Drug Research Laboratories, Inc,[115] 1982d
7.3%	RIPT in 53 subjects	Low-grade sensitization or cumulative irritation in 15 subjects, sensitization in 6	Food and Drug Research Laboratories, Inc,[115] 1982d
7.3%	RIPT in 53 subjects	Low-grade sensitization or cumulative irritation in 24 subjects, sensitization in 13	Food and Drug Research Laboratories, Inc,[115] 1982d
2% aqueous	21-day patch test in 25 subjects; single patch challenge	Intense irritation reactions in all subjects in first 10 days; positive reactions in all subjects at challenge	Rapaport,[117] 1983

(continued)

Table 12. (continued)

Concentration	Procedure	Results	Reference
22.6%	RIPT in 101 subjects	39 irritation reactions at induction and 17 reactions at challenge	International Research Services, Inc,[116] 1983
22.6% induction, 2.3% challenge	RIPT in 103 subjects	6 irritation reactions at induction and 2 reactions at challenge	Food and Drug Human Clinical Laboratories, Inc,[118] 1984
14%-15.4% (pH 6.5-6.9)	Two 48-h applications in 100 subjects	No skin irritation	Springer et al,[99] 1985
14%-15.4% (pH 6.5-6.9)	RIPT in 103 subjects	No irritation or sensitization	Springer et al,[99] 1985
7.88% (pH 7)	RIPT in 193 subjects	147 reactions at induction and 76 at challenge (original site) and 44 (remote site)	UCLA,[99] 1985b
23.4%	RIPT in 205 subjects	46 reactions at induction and/or first challenge	Essex Testing Clinic, Inc,[107] 1990a
23.4%	RIPT in 199 subjects	68 reactions at induction and/or first challenge	Essex Testing Clinic, Inc,[107] 1990a
21.6%	RIPT in 52 subjects	4 reactions at induction and 3 reactions at challenge	Essex Testing Clinic, Inc,[108] 1990b
18%	RIPT in 55 subjects	4 reactions at induction and 1 at challenge	Essex Testing Clinic, Inc,[108] 1990b
14.4%	RIPT in 55 subjects	2 reactions at induction and 2 reactions at challenge	Essex Testing Clinic, Inc,[108] 1990b
10.8%	RIPT in 58 subjects	3 reactions at induction and 1 reactions at challenge	Essex Testing Clinic, Inc,[108] 1990b
		Potassium Thioglycolate	
6.88% in depilatory	10-min application in 20 subjects	No adverse effects	CTFA,[21] 2007b
6.88% in depilatory	Efficacy study in 160 subjects	No adverse effects	CTFA,[21] 2007b
6.88% in depilatory	7-min application in 20 subjects	No adverse effects	CTFA,[21] 2007b
		Thioglycolic Acid	
4.5% in lotion base	10-min application in 45 patients	No irritation	Bagshaw et al,[38] 1980
4.5% in lotion base	10-min application in 45 patients: pubic, perianal, and scrotal areas	11 patients had hot sensation around scrotum	Bagshaw et al,[38] 1980

Thioglycolate (pH 9.6).[95] Patches remained in place for 1 hour. 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 hours. Skin irritation was not observed in any of the subjects.

A 6.5 % Ammonium Thioglycolate solution was applied to the skin of 154 subjects daily for a period of 2 months.[58] The duration of each application ranged from 40 to 60 minutes. Skin irritation was not noted in any of the subjects.

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.[96] All subjects were patch tested (48-hour exposures) with 0.5N, 1.0N, and 1.5N solutions of Ammonium Thioglycolate (the authors stated that a 1.0N solution of Ammonium Thioglycolate is approximately 11% Ammonium Thioglycolate). Faint erythema (1 patient) and erythema (2 patients) were observed at sites patch tested with 1.0N Ammonium Thioglycolate. The following reactions were observed at sites tested with 1.5N 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 0.5N Ammonium Thioglycolate.

Ammonium Thioglycolate (1:100 dilution) was applied intradermally to 14 atopic patients (13-60 years old).[97] 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+).

The skin irritation potential of 2 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).[98] 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 hour. Reactions were scored 2 to 3 minutes 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.

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.[99] In another study, a patch containing 0.15 mL of the lotion was applied to the skin of each of 100 subjects and removed after 48 hours. Sites were graded for signs of irritation 15 and 24 hours 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.[100]

Potassium Thioglycolate

In a summary provided by the CTFA, 3 studies performed with a depilatory leg crème containing 6.88% Potassium Thioglycolate were described.[21] In the first study, a clinical safety and efficacy test was performed to compare a prototype depilatory leg crème containing Potassium Thioglycolate with a commercial product, with 1 product used on each leg of the subjects. Twenty subjects started and completed the study. The depilatory response was evaluated every minute starting at 3 minutes after application until 10 minutes after application. The test sites were evaluated before application of the products, immediately after removal of the products, and 10 minutes after removal of the products. No adverse effects were reported and no signs of scaling, edema, or irritation were noted during the study. The second study was performed to determine the efficacy of the same prototype depilatory leg crème with a commercial product. No adverse events were observed in the 160 subjects that completed the study. The third study was an efficacy test on another depilatory leg crème that contained 6.88% Potassium Thioglycolate that compared the duration of hair removal between depilatory use and shaving with a razor. Twenty subjects started and completed the study. The leg crème was applied for 7 minutes and the skin was evaluated on days 3 to 7 after application. The evaluation at days 3 to 7 after application did not report any adverse events.

Thioglycolic Acid

A lotion base containing 4.5% Thioglycolic Acid was applied to a 2 × 2-cm area on each of 45 patients.[38] Sites were rinsed 10 minutes later. None of the subjects had signs of inflammation. After a 12-hour interval, the lotion was applied to pubic, perineal, and scrotal regions, and sites were rinsed 10 minutes 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.

Dermal Irritation and Sensitization

Depilatories containing thioglycolates are reportedly irritants, but rare sensitizers and cause contact epilating folliculitis when used improperly.[101] Glyceryl Thioglycolate in permanent wave solutions has become a major allergen in hairdressers with fewer reactions reported and somewhat less in the clients. Glyceryl Thioglycolate persists on treated hair for weeks or months, and is a common sensitizer. Ammonium Thioglycolate, a rare sensitizer, is found in professional, home permanents and hair straighteners.

Ammonium Thioglycolate

Patch tested 268 patients (143 males, 143 females) with a hair waving lotion (pH 9.21) containing 4.61% Thioglycolic Acid and 0.86% ammonia were studied.[93] Patches remained in place for periods ranging from 48 hours 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. A group of 863 subjects was also patch tested with a hair waving lotion (same as above) containing 4.61% Thioglycolic Acid and 0.86% ammonia. 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 5 and 3 cold waves, respectively.

A group of 223 subjects (18-34 years old, normal skin) was patch tested with 0.55N Ammonium Thioglycolate (≥6.0% solution, pH 9.3).[102] 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 hours after application, and sites were graded. Sites also were graded approximately every 48 hours 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 0.55N Ammonium Thioglycolate (same procedure), 26 had an immediate reaction. One of the 26 subjects had a delayed reaction. It was concluded that 0.55N Ammonium Thioglycolate induced skin irritation and sensitization.

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.[81] 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 hours. 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 hours, and reactions were scored at 48 and 96 hours. Sensitization reactions were not observed in any of the subjects.

The skin irritation and sensitization potentials of a cold wave product (pH 9.3-9.5) containing 9.0% Ammonium Thioglycolate using 52 subjects (29-77 years old) was evaluated in a Repeated Insult Patch Test (RIPT).[103] 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 hours, 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 hours. Sites were scored (same scale) 48 and 72 hours after application. Reactions to the

product were not observed at any time during the study. The product was neither an irritant nor a sensitizer.

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%) was evaluated using 54 subjects (18-67 years old).[104] The solution was applied for 24 hours either to the inner aspect of the arm or to the back, via an occlusive patch. A total of 10 applications were made to each subject. Patch removals on Tuesdays and Thursdays were each followed by a 24-hour nontreatment period. Patch removals on Saturdays were each followed by a 48-hour 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 hours. Sites were scored (same scale) 24 and 48 hours 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.

The skin irritation and sensitization potential of another cold wave product (pH 7.3-7.6) containing 17.5% Ammonium Thioglycolate was evaluated using 102 subjects (15-73 years old) according to the procedure stated immediately above.[105] 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.

An evaluation of the skin irritation and sensitization potential of a permanent waving solution containing 12.0% Ammonium Thioglycolate, 5.0% urea, and 0.61% ammonium hydroxide was performed using a modification of the Draize-Shelanski-Jordan patch test.[106] 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-hour applications. After a 13-day nontreatment period, a challenge patch was applied for 48 hours to the back of each subject. A second challenge patch was applied (48-hour contact period) 7 days later. Challenge sites were scored 48 and 72 hours after application. Reactions were scored according to the scale: 0 (no reaction) to 4 (intense erythema with edema and vesicles). The following reactions 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%.

The skin irritation and sensitization potential of a permanent waving solution containing 7.1% Ammonium Thioglycolate, 5.0% urea, and 1.20% ammonium hydroxide was evaluated using 211 subjects, according to the procedure stated immediately above.[107] 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.

The skin irritation and sensitization potential of 18.0% Ammonium Thioglycolate in a modified RIPT

was evaluated using 220 healthy subjects (25 males, 195 females, 18-66 years old).[108] 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 × 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-hour applications. Patch removals on Tuesdays and Thursdays were each followed by a 24-hour nontreatment period, and those on Saturday by a 48-hour 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 hours to a new test site on each subject. Reactions generally were scored at 24 and 48 hours after application. Three of the original 220 subjects were disqualified because of reactions, more severe than mild erythema, to 1 or both test substances during the first 3 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 more severe 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 hours, but not at 48-hours after application. The third subject had no reactions at 24 hours, barely perceptible erythema at 48 hours, and latent, moderate erythema at 72 hours after application. The authors concluded that 18.0% Ammonium Thioglycolate was a very mild to moderate irritant in approximately 47% (96 of 205) of the population tested, and 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.

In another study in the same testing facility, following the same protocol described above, the skin irritation and sensitization potential of 18.0% Ammonium Thioglycolate was evaluated in a modified RIPT using 220 healthy subjects (24 males, 196 females, 18-69 years old).[108] A total of 199 of the original 220 subjects completed the test procedure. Two subjects were disqualified because of reactions to 1 or both test substances, after the first 3 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 this 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). Moderate erythema was the most severe reaction 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 hours after application and moderate erythema and edema at 72 hours, 1 subject with no reactions at 24 and 48 hours and barely perceptible erythema at 72 hours, and 1 subject with no reactions at 24 hours, 48 hours, or 72 hours. The authors concluded that 18.0% Ammonium Thioglycolate induced very mild to marked irritation in approximately 27% (54 of 199) of the population tested. 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.

RIPTs 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).[109] A panel of 240 subjects was patch tested with 14.4% Ammonium Thioglycolate, and 4 groups of 60 subjects (same 240 subjects) were patch tested with

10.8%, 14.4%, 18.0%, and 21.6% Glyceryl Thioglycolate, respectively.

On Mondays, Wednesdays, and Fridays, the test substance was applied (0.2 mL, semi-occlusive patch) for 24 hours 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-hour nontreatment period, and removals on Saturday by a 48-hour 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 9 applications. After a 15- to 19-day nontreatment period, challenge patches were applied to new test sites. Reactions were scored at 24 and 48 hours after application. 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 the 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-hour challenge readings. In these subjects, reactions were not observed during 48-hour 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 2 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-hour 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 nor was there any evidence of induced allergic contact dermatitis in human subjects.

Glyceryl Thioglycolate

The skin irritation and sensitization potential of an acid wave product (pH 6.9-7.2) containing 22.6% Glyceryl Thioglycolate was evaluated in an RIPT of 52 subjects (29-77 years old).[110] 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 hours, 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 hours. Sites were scored (same scale) 48 and 72 hours after application. Reactions to the product were not observed at any time during the study. The product was neither an irritant nor a sensitizer.

The skin irritation and sensitization potential of a waving lotion (pH 6.9-7.2) containing 22.6% Glyceryl Thioglycolate was evaluated in an RIPT of 52 subjects (12-68 years old).[111] A 25% aqueous solution of the lotion (effective concentration of Glyceryl Thioglycolate 5.7%) was applied to each subject via occlusive patches. 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.

Another RIPT was conducted to evaluate the skin irritation and sensitization potential of a 25.0% aqueous solution of 80.2% Glyceryl Thioglycolate (effective concentration of Glyceryl Thioglycolate 20.1%) using 29 subjects (14-74 years old).[22] The solution was applied, either to the inner aspect of the arm or to the back (between scapulae and waist), for 24 hours via an occlusive patch. Ten applications were made to each subject. Patch removals on Tuesdays and Thursdays were each followed by a 24-hour nontreatment period. Patch removals on Saturdays were each followed by a 48 h non-treatment 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 hours. Sites were scored (same scale) 24 and 48 hours 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).

A modified RIPT was used to evaluate the skin irritation and sensitization potential of Glyceryl Thioglycolate (2% in petrolatum).[112] A total of 51 subjects (23-68 years old) were tested. Initially, the test substance was applied for 48 hours to the back of each subject via an occlusive patch. The test substance was then applied (24-hour contact period) on alternate days for a total of 10 applications. Sites were graded at the end of each 24-hour period. After a 13-day nontreatment period, a challenge patch was applied for 48 hours to the back of each subject. A second challenge patch was applied (48-hour contact period) 7 days later. Challenge sites were graded 48 and 72 hours 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 authors attributed all the reactions to irritation and not sensitization.

Skin irritation in 31 of 53 subjects (23-68 years old) tested (same procedure) with 2% aqueous Glyceryl Thioglycolate was reported.[113] 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 reactions ranging from mild erythema to intense erythema with edema only during induction and challenge phases, respectively. The authors attributed all the reactions to irritation and not sensitization.

The skin irritation and sensitization potential of 4% Glyceryl Thioglycolate (in petrolatum) was determined in 52 subjects (23-68 years old) using the same procedure in the previously reported study.[114] 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 authors attributed all the reactions to irritation and not sensitization.

Skin irritation (same procedure) in 37 of 51 subjects (23-68 years old) tested with 4% aqueous Glyceryl Thioglycolate was reported.[115] 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.

The skin irritation and sensitization potential of an acid wave product containing 22.6% Glyceryl Thioglycolate (pH 6.9-7.2) using 53 subjects (17-73 years old) was evaluated in a modified RIPT.[116] The product was applied at 33.0% (effective concentration of Glyceryl Thioglycolate 7.5%) to the back of each subject via a semi-occlusive patch for 24 hours. Sites were then scored during a 24-hour 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 hours. The second challenge patch was applied (48-hour period) 1 week after application of the first. Sites were scored (same scale) immediately after patch removal. Skin reaction patterns indicative of sensitization and/or cumulative irritation were observed in 27 subjects.

In a similar study (same procedure), International Research Services, Inc evaluated the skin irritation and sensitization potentials of an acid wave product (pH 6.9-7.2) containing 22.6% Glyceryl Thioglycolate using 101 subjects and in an RIPT.[117] 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.

A 21-day skin irritation test was conducted with 25 subjects.[118] 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. The author stated that these results are compatible with irritant contact dermatitis.

The skin irritation and sensitization potential of an acid wave product (22.6% Glyceryl Thioglycolate) was evaluated using an RIPT.[119] A total of 103 subjects were tested (18-74 years old). The product was applied for 24 hours to the back (between scapulae and waist) of each subject. Patch removals on Tuesdays and Thursdays were followed by 24-hour nontreatment periods. Patch removals on Saturdays were followed by 48-hour 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 9 applications. After a 12- to 17-day nontreatment period, challenge patches were applied to new sites. Sites were scored (same scale) 24 and 48 hours 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 hours after application of the challenge patch. The product did not induce allergic contact dermatitis in any of the subjects.

The skin irritation and sensitization potential of an acid permanent waving solution containing 15.76% Glyceryl Thioglycolate (pH 7.0) was evaluated using a modified RIPT.[120] 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 hours. Reactions were scored immediately after patch removal according to the scale: 0 (no reactions) to 4 (intense erythema with edema and vesicles). This procedure was repeated on Monday through Friday for a total of 10 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 hours. 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-hour 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 hours later. A total of 147 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 authors attributed all the reactions to irritation and not sensitization.

The skin irritation and sensitization potential of a permanent waving lotion (pH 6.5-6.9) containing 14% to 15.4% Glyceryl Thioglycolate was evaluated according to a modified RIPT.[99] A semi-occlusive patch containing 0.5 mL of the lotion was applied to each of 103 subjects. After 48 hours of contact, patches were removed and sites were scored for signs of irritation. This procedure was repeated for a total of ten 48-hour exposures. After a 14-day nontreatment period, a challenge patch was applied (48-hour exposure) to each subject. Sites were then scored. The lotion induced neither irritation nor sensitization in any of the subjects.

The skin irritation and sensitization potential of 23.4% Glyceryl Thioglycolate was evaluated in a modified RIPT using 220 healthy subjects (25 males, 195 females, 18-66 years old) using the same protocol described earlier for Ammonium Thioglycolate.[107] Three of the original 220 subjects were disqualified because of reactions, more severe than mild erythema, to 1 or both test substances during the first 3 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 observed in 46 subjects during the induction and/or the first challenge phase of the study. During the first challenge, 2 subjects had reactions that were classified as mild erythema (score = 1). Reactions more severe 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 hours after application, and no reactions were observed at 48 hours. The authors concluded that 23.4% Glyceryl Thioglycolate was a very mild to moderate irritant in approximately 22% (46 of 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.

In another study by this same testing facility, the skin irritation and sensitization potential of 23.4% Glyceryl Thioglycolate was evaluated in a modified RIPT using 220 subjects (24 males, 196 females, 18-69 years old) using the same protocol.[107] Two subjects were disqualified because of reactions to 1 or both test substances, after the first 3 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, 68 had barely perceptible to marked erythema during induction and/or the first challenge phase. During the first challenge, 5 subjects had reactions that were classified as mild erythema (score = 1), 1 subject had mild and moderate erythema (score = 2), and 1 subject had moderate erythema. Reactions more severe 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 hours after application, mild erythema with mild edema at 48 hours, and no reactions at 72 hours; 1 subject with mild erythema at 24 hours, mild erythema with mild edema at 48 hours, and moderate erythema with mild edema at 72 hours; 1 subject with moderate erythema and mild edema at 24 and 48 hours and mild erythema with mild edema at 72 hours; 1 subject with nonerythematous papular eruptions at 24, 48, and 72 hours; 1 subject with no reactions at 24 hours and barely perceptible erythema at 48 and 72 hours; 1 subject with transient, mild erythema with papular eruptions at 48 hours and papules and no erythema at 72 hours. The authors concluded that 23.4% Glyceryl Thioglycolate induced very mild to marked skin irritation in approximately 34% (68 of 199) of the population tested. Also, the results of initial RIPT of the 199 subjects and the second challenge patch test involving 6 subjects suggested that 4 subjects (4 of 199) had possible low- to moderate-grade irritant sensitivity and that 2 subjects had possible and probable moderate-grade induced allergic contact dermatitis, respectively.

The skin irritation and sensitization potential of 21.6% Glyceryl Thioglycolate was evaluated using an RIPT in a total of 60 subjects (18-69 years old) and in the same protocol described above.[108] 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 reactions 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 2 induction applications were observed. Three subjects had reactions, barely perceptible erythema (24-hour reading), only during the challenge phase. The authors concluded that 21.6% Glyceryl Thioglycolate did not induce clinically meaningful irritation nor was there any evidence of induced allergic contact dermatitis in human subjects.[108]

This testing facility also reported results of an RIPT to evaluate the skin irritation and sensitization potential of 18.0% Glyceryl Thioglycolate in a total of 60 subjects (18-69 years old) using the same procedure.[108] 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 reactions, barely perceptible erythema (score = +), to 18.0% Glyceryl Thioglycolate only during the induction phase. Reactions to not more than 2 induction applications were observed. One subject had a reaction, barely perceptible erythema, to 1 induction application of 18.0% Glyceryl Thioglycolate, mild erythema (score = 1, 48-hour reading) during the first challenge and barely perceptible erythema (24-hour 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.

This testing facility reported results of another RIPT using 14.4% Glyceryl Thioglycolate in a total of 60 subjects (18-69 years old), again with the same procedure.[108] 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-hour challenge readings. In these subjects, reactions were not observed during 48-hour challenge readings nor during the induction phase. Two of the 55 subjects had reactions, barely perceptible erythema (score = +), to 14.4% Glyceryl Thioglycolate only during the induction phase. Reactions to 1 induction application were observed. Additionally, 2 subjects had reactions only during the challenge phase. One subject had barely perceptible erythema (24-hour reading), and the second subject had moderate erythema with mild to moderate edema (score = 2e, 24-hour reading), marked erythema with mild to moderate edema and papules (score =3ep, 48-hour reading), and severe erythema with mild to moderate edema (score = 4e, 72-hour reading). During the second challenge, this subject had severe erythema with mild to moderate edema (score = 4e, 24- and 48-hour readings) and marked erythema with mild to moderate edema (score = 3e, 72-hour 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.

In this same report by this testing facility, the skin irritation and sensitization potential of 10.8% Glyceryl Thioglycolate was evaluated using 60 subjects (18-69 years old) according to the procedure in the preceding paragraph.[108] Three of the 58 subjects had reactions to 10.8% Glyceryl Thioglycolate only during the induction phase. Reactions to not more than 3 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 = +, 24-hour 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.

Dermal Sensitization

Ammonium Thioglycolate

The sensitization potential of Ammonium Thioglycolate in 85 patients was evaluated using the epicutaneous test.[71] 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.

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.[65] A group of 20 subjects served as the control. The concentrations of Ammonium Thioglycolate tested ranged from 0.3% to 7%. In open patch tests, positive reactions were noted in 1 subject patched with 3%, 1 subject patched with 5%, and 2 subjects patched with 7%. In closed patch tests, 5 subjects patched with 3%, 5 subjects patched with 5.0%, and 8 subjects patched with 7% had positive reactions. In the control group, 4 and 5 subjects had positive reactions to 5% and 7% Ammonium Thioglycolate, respectively.

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.[97] Pharyngeal irritation lasted 0.5 to 2 hours, depending on the degree of sensitivity of the patient. Eight control patients (nonasthmatic and nonatopic) did not have positive reactions to the test substance.

Nasal provocation tests were performed on hairdressers suffering from occupational rhinitis.[121] One patient of 31 responded positive to a 0.6% Ammonium Thioglycolate solution pH 7.00.[122]

Treatment Effects

A study using a randomized selection of 92 patients who underwent hair removal before a medical operation was conducted.[123] The subjects either were shaved or used a depilatory cream containing 5% Calcium Thioglycolate. There was no difference in occurrence of pathogenic bacteria or on wound healing. The patients that underwent shaving had some skin damage, discomfort, and were not allowed to perform hair removing procedure by themselves. Patients who used the depilatory cream did not report discomfort and were allowed to apply the cream themselves under observation.

A Thioglycolic Acid (4.5% wt/wt with pH of 12-12.5) containing spray or lotion was used for preoperative preparation of the scrotum and perineum of 45 patients.[38] Of these, 33 patients had no irritation and 11 noted a "hot" feeling. Twenty-six patients had previously undergone the preoperative razor shaving and 85% of the patients preferred the Thioglycolic Acid containing preparations. Four patients did not prefer the Thioglycolic Acid containing preparations because they felt it was "messy." Four patients had hair-bearing skin inlay urethroplasty (hair in the urethra) and placed Thioglycolic Acid containing preparations in the urethra for 10 to 30 minutes. These patients reported discomfort on voiding the bladder that lasted for 24 hours and caused some edema of mucosa in the navicular fossa. However, all evidence of discomfort disappeared by 36 hours and there were no systemic or late complication reactions reported.

Occupational Exposure

During a 3-month period, 7 hairdressers with dermatitis (on hands) were patch tested with 2.5% Glyceryl Thioglycolate in petrolatum.[124] Five subjects developed allergic contact dermatitis. Allergic reactions were not observed in 47 control subjects.

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.[125] All of the patients were employed as hairdressers. Glyceryl Thioglycolate induced allergic reactions in 6 subjects.

Eight hairdressers (average age 31 years) and 4 clients (average age 57 years) developed allergic reactions to a permanent wave formulation containing Glyceryl Thioglycolate.[126] 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 hours. Sites were graded 30 minutes and 7 days after patch removal. Only reactions 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 12th 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.

Four hairdressers with eczematous dermatitis had a positive reaction to a cold permanent wave solution containing 5% Ammonium Thioglycolate, which disappeared within 96 hours.[127] Open patch tests were performed using 5% and 2% Ammonium Thioglycolate. All patients reacted positively to both concentrations. Eighteen healthy subjects and 2 hairdressers without dermatitis had open patch tests to the 5% solution and reacted negatively.

Seven beauticians (16-20 years old) with hand dermatitis were patch tested (open patches) with an aqueous solution of 5% Ammonium Thioglycolate.[128] Allergic reactions were observed in 3 subjects at 48 hours after application.

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).[129] 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 5 beauty salon clients who were not in either experimental group, were collected immediately before and after application of the permanent and at 2 weeks, 6 weeks, and 3 months after application. Prior to the study, the 5 beauty salon clients had not had their hair dyed, tinted, or permanent waved within the last year. The test substances were applied for 48 hours to the upper back of each subject via Finn chambers secured with porous tape. Sites were scored 30 minutes 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 permanent 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 permanent (3 subjects), and tresses 3 months after permanent (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 permanent had been applied. There was no evidence of skin irritation or sensitization in any of the subjects tested.

Of 99 hairdressers patch tested, 18 gave allergic reactions to 1% Glyceryl Thioglycolate in petrolatum, but only 11 of these reacted positively to 0.5% pet Glyceryl Thioglycolate.[130] In a consecutive series of 1261 patients being patch tested, 25 reacted to 1% Glyceryl Thioglycolate in petrolatum and 18 of these reacted to 0.5% Glyceryl Thioglycolate in petrolatum.

Of a total of 809 hairdressers patch tested in Europe, 4% were positive to Ammonium Thioglycolate, 19% had a positive reaction to Glyceryl Thioglycolate, and 3 of 8 had a positive reaction to Glyceryl Thioglycolate through vinyl gloves.[131]

London hairdressers (n = 143) were patch tested with eczema (18 men and 125 women).[132] Glyceryl Thioglycolate (0.5%-1% concentration) produced positive reactions in eczematous atopics (23 of 45, 51%), mucous membrane atopics (12 of 32, 38%), and nonatopic (27 of 66, 41%) individuals. Ammonium Thioglycolate (1%-2.5% concentrations) showed positive results displayed as eczematous atopic (4 of 45, 9%), mucous membrane atopic (2 of 32, 6%), and nonatopic (5 of 66, 8%) responses.

Hairdressers with contact dermatitis (n = 106, 1985-1994 in Greece) were patch tested with Glyceryl Thioglycolate 2.5% and 2.5% Ammonium Thioglycolate, both in petrolatum; 5.6% (6 people) had positive reactions to Glyceryl Thioglycolate and 11.3% (12 people) had positive patch-test results to Ammonium Thioglycolate, with an additional 3 subjects having irritant reactions.[133]

In the Netherlands, patch tests of 103 hairdressers resulted in 2 positive reactions to a 2.5% Ammonium Thioglycolate solution and 59 positive reactions to a 1% Glyceryl Thioglycolate.[134]

Ten hairdressers with exposure to permanent wave solutions containing thioglycolate (exact composition not specified) for 10 to 30 years experienced vertigo, tinnitus, or hearing loss were studied.[93] Seven patients had sensorineural hearing loss after pure tone audiometry. Eye tracking abnormalities were seen in 3 patients, 2 had nystagmus, 5 had vertigo, 5 had tinnitus, and 7 had abnormalities in a vestibuloocular caloric test.

Several retrospective analyses of occupational exposures were performed.[55] A retrospective analysis (1980-1987) of 2449 cases of possible occupational

skin disease in Western Australia found 368 cases of allergic contact dermatitis related to occupational exposure. Of the 368 cases, 12.5% were attributed to Glyceryl Thioglycolate exposure, which was the third most frequent allergen (behind nickel at 25% and thiuram at 15%). Another retrospective analysis (1985-1990) in Italy identified 302 hairdressers with contact dermatitis, mainly on the hands. Of the 302 patients, 184 were patch tested; 1% Glyceryl Thioglycolate in petrolatum elicited positive reaction in 34 of the 184 hairdressers (sensitization rate 11.3%). In a retrospective analysis (1990-1999), 209 Italian hairdressers were patch tested with the hairdresser's series. Positive reactions to Glyceryl Thioglycolate occurred in 25 of the hairdressers. A retrospective analysis of 191 German hairdressers found positive reactions to Glyceryl Thioglycolate in 34% of the subjects. Two retrospective analyses reviewed the patch test results (1992-1998 and 1996-1998) of 1336 and 597 patients, respectively, that were at one time employed as hairdressers in Germany. In the first study, 1% Glyceryl Thioglycolate (petrolatum) elicited positive patch test responses in 45% of the patients in 1992 to less than 20% in 1998. In the second study, Glyceryl Thioglycolate (concentration not provided) had positive patch response in 20.2% of the patients. The authors noted that the sensitization rate decline was possibly due to the removal of Glyceryl Thioglycolate from hairdressing products in Germany. In a group of 66 individuals suspected of allergic reactions, 8 were identified as hairdressers. These 8 subjects were patch tested with 2.5% Glyceryl Thioglycolate (petrolatum). Of the 8 hairdressers, 5 had a positive response. In a retrospective analysis of 178 hairdressers in Germany, Glyceryl Thioglycolate was a leading allergen with a sensitization grade of 30.9%. A final retrospective analysis (between 1995 and 2002) identified 2506 patients with hand dermatitis to hairdressing cosmetics and hair care products. Of this group, 884 were or had been employed as hairdressers and 1217 were female clients of hairdressers. Most of these 2101 patients (95.8% of the hairdressers and 80.1% of the clients) were patch tested with the hairdresser's series. During the analysis, a decline of contact allergy to Glyceryl Thioglycolate was observed in the hairdressers from 31.2% to 8.5% in the time period between 1995/1996 and 2001/2002. The sensitization rate of Glyceryl Thioglycolate in female clients varied between 0.9% and 2.3% without any trends.

Occupational Exposure Limits

The threshold limit value (TLV) established by the American Conference of Governmental Hygienists (ACGIH) for dermal and inhalation exposure to Thioglycolic Acid from air is 1 ppm.[135] Dermal irritation is the critical effect on which ACGIH based its TLV.

Other Patch Testing

Ammonium Thioglycolate

In Italy from 1985 to 1990, 261 frequent hairdresser clients, all of whom had dermatitis, were examined (5 male and 256 female). Sensitization to Ammonium Thioglycolate (2.5% petrolatum) was found in 3 (1.1%) of the patients by conducting patch tests.[136]

Of 475 patients with contact allergy tested in Europe, 1 person had a positive reaction to Ammonium Thioglycolate.[137]

Glyceryl Thioglycolate

Patients with cosmetic-related dermatitis (n = 403) with 2.5% Glyceryl Thioglycolate were tested over a period of 64 months (1977-1983).[138] Patch tests were applied to the upper back of each patient and removed after 48 hours. In most patients, sites were graded 48, 72, 96, and 120 hours after patch application. Allergic sensitization reactions were observed in 25 subjects.

Positive patch tests for hair care products and depilatories containing Glyceryl Thioglycolate (concentration not provided) were seen in 7 of 79 people in Sweden (1989-1994).[139]

Patients with contact allergy were tested in Europe (n = 475), in which 9 had a positive reaction to glyceryl monothioglycolate (concentration not provided).[136]

Significance-prevalence index numbers (SPIN) that were calculated for data collected by the North American Contact Dermatitis Group (NACDG; 1984-1996) in each of 2 groupings, 1984-1994 and 1994-1996, were reported.[140] Relevance (R) was reported as "definite," "probable," or "possible." The calculations were:

$SPIN_{94\text{-}96}$ = (proportion of allergic population)* (1* $R_{definite}$ + 0.66*$R_{possible}$ + 0.33*$R_{probable}$)*1000

$SPIN_{84\text{-}94}$ = (proportion of allergic population)* (0.66*$R_{present}$)*1000

The ranking for 1% Glyceryl Thioglycolate increased from 27 (1984-1994) to 17 (1994-1996) as calculated by SPIN.

Case Reports

The case of a 39-year-old woman with a history of 1.5 years of episodic rhinitis and laryngitis who reported occurrence of chest heaviness and dyspnea beginning 4 to 8 hours after work at a beauty salon was recorded.[141] She was a nonsmoker with no history of allergic respiratory disease or sinobronchitis. Allergy skin testing (pricking) and intradermal methods provided no reaction to a wide variety of allergens. The patient underwent provocative tests to permanent wave solution (no specifics about the composition of the solution were provided). Increased nasal airway resistance occurred by 5 minutes after cessation of 5 minutes of exposure. The patient experienced a headache, a sense of nasal congestion, and a sense of tightness in the chest. Treatment with self-pump cromolyn solution decreased the reaction slightly. A second patient 40 years of age had a 2-year history of both nasal and chest symptoms. She owned and operated a salon for 10 years and smoked 1 pack of cigarettes per day for 7 years. Results of allergy skin tests for a wide variety of environmental allergens were negative. This patient, after provocative tests using the permanent wave solution, developed nasal resistance within 15 minutes of cessation of exposure. Four normal adult patients had no significant change after exposure to permanent wave solution. No detailed information regarding contents of this solution were available.

Ammonium Thioglycolate

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.[142] During month 8 the hairdresser was patch tested (open patches) with 7 different cold wave solutions containing 0.3%, 0.5%, 0.7%, 1%, 3%, 5%, and 7% aqueous Ammonium Thioglycolate. Moderately strong positive reactions to all 7 wave solutions were observed 24, 48, and 72 hours after application. Erythema and swelling were observed 6 hours after application of 7% and 5% Ammonium Thioglycolate and 24 hours after application of 3% Ammonium Thioglycolate. All positive reactions persisted for more than 1 week. 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 2 shampoos, 2 hair rinses, and 4 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 hours after application. Reactions to the shampoos, hair rinses, and hair treatments were not observed. The authors concluded that allergic reactions observed in the hairdresser were due to Ammonium Thioglycolate.

The case of a 20-year-old woman with a history of rhinoconjunctivitis, who had worked as a hairdresser for 4 years, was reported.[143] She noticed a worsening of preexisting irritant hand dermatitis after contact with permanent waving solution containing 0.5% to 4.0% ammonium thiolacetate and 6.0% to 10.5% Ammonium Thioglycolate. She had papulovesicular eczema, with fissures and erosions, white dermographism, and dry scaly skin of the fingers and hand.

Calcium Thioglycolate

One patient who applied a depilatory to the scrotum experienced a severe irritation.[144] A second man used a depilatory to remove suprapubic and scrotal hair. The suprapubic area had no reaction, but the scrotal tissue had a severe reaction that ulcerated. It was suggested that some Calcium Thioglycolate remained in the folds of the scrotal skin and sulfur dioxide may have formed.

Glyceryl Thioglycolate

Glyceryl Thioglycolate (2.5% aqeous) caused 6 cases of contact dermatitis, 3 in hairdressers and 3 in women who have received permanent waves.[145] Additionally, 1 of the hairdressers was sensitized to Ammonium Thioglycolate (2.5% petrolatum) as well. All patch tests through vinyl gloves were positive in hairdressers.

A hairdresser showed a positive patch test result to Glyceryl Thioglycolate (concentration not provided).

A 30-year-old female hairdresser had chronic idiopathic urticaria.[146] The hives appeared a few days after a permanent wave solution container, containing 80% aqueous solution of glyceryl monothioglycolate (Glyceryl Thioglycolate), ruptured, spraying her face, chest, and arms. She had a positive urticarial response (>10 mm) to saline dilutions of

Glyceryl Thioglycolate 1:12,500. Despite 7 years of exposure to Glyceryl Thioglycolate as a hairdresser the patient never developed a delayed (type IV) eczematous response to Glyceryl Thioglycolate either clinically or upon patch testing.

HAIR DYE EPIDEMIOLOGY

Hair dyes may be broadly grouped as oxidative (permanent) and direct (semipermanent). The oxidative dyes consist of precursors mixed with developers to produce color, while direct hair dyes are a preformed color. Ammonium Thioglycolate and Thioglycolic Acid are used as oxidative hair dye components.

While the safety of individual hair dye ingredients is not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information and have been considered by the CIR Expert Panel.

In 1993, an International Agency for Research on Cancer (IARC) working group evaluated 78 epidemiology literature citations and concluded that "personal use of hair colourants cannot be evaluated as to its carcinogenicity" and that "occupation as a hairdresser or barber entails exposures that are probably carcinogenic."[147] The IARC report did not distinguish between personal use of oxidative/permanent versus direct hair dyes, or distinguish among the multiple chemical exposures in addition to hair dyes to which a hairdresser or barber might be exposed.

The available epidemiology literature published from 1992 through February 2005 was reviewed, including more than 80 citations on personal hair dye use published since the IARC review.[148] The authors found that hair dye exposure assessment ranged from ever/never use to information on type, color, and duration and frequency of use. The authors found insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers. The review highlighted well-designed studies with an exposure assessment that included hair dye type, color, and frequency or duration of use, which found associations between personal hair dye use and development of acute leukemia, bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma. These findings, however, were not consistently observed across studies.

The CIR Expert Panel did specifically note reports from a case-control study, which did suggest a possible genetically susceptible subgroup, which detoxify arylamines to a lower degree than the general population.[149] The study authors hypothesized that this subgroup may be at greater risk of bladder cancer from hair dye exposure.

Several studies published since the Rollison et al review[148] also have been considered. Discussion of the available hair dye epidemiology data is also available at http://www.cir-safety.org/findings.shtml.

Bladder cancer. A study by Kelsey et al was a follow-up to the previously published case-control study in New Hampshire and examined the links between those bladder cancer cases with an inactivated tumor suppressor gene (TP53) and various exposures.[150,151] Hunchareik and Kupelnick performed a meta-analysis of 6 case-control and 1 cohort study.[152] Takkouche et al performed a meta-analysis of 9 personal use case-control studies and 1 cohort study.[153] Ji et al reported a cohort occupational study that included hairdressers.[154] Kogevinas et al presented evidence from a case-control study in Spain.[155] Lin et al presented a case-control study of personal permanent hair dye use.[156] Serretta et al reported preliminary results from a multicentric study of risk factors in Ta-T1 transitional cell carcinoma of the bladder, including hair dye use.[157] Pelucchi et al reviewed data on bladder cancer mortality rates and then recognized potential environmental (including hair dye exposures) and genetic risk factors.[158] Bolt and Golka reviewed the published literature on bladder cancer risk and personal use of hair dyes (17 publications) or occupation as a hairdresser and/or barber (23 publications).[159]

Lymphoma and leukemia. Takkouche et al reported a meta-analysis of reports of hematopoietic cancers (19 publications).[153] Mester et al reviewed 10 epidemiology studies regarding the relationship between occupational exposure in hairdressing and diseases of the malignant lymphoma group.[160] A case-control study in Spain by Benavente et al examined the association between lifetime hair dye exposure with various lymphomas, including chronic lymphocytic leukaemia.[161] de Sanjosé et al reported on the association between personal use of hair dyes and lymphoid neoplasm using data from a European

multicenter case-control study.[162] Chiu et al evaluated non-Hodgkin's lymphoma subtypes defined according to the presence or absence of t(14:18) translocation as a function of smoking, familial hematopoietic cancer, and hair dye use.[163] Morton et al examined the risk of non-Hodgkin's lymphoma as a function of hair dye use and genetic variation in N-acetyltransferase 1 (*NAT1*) and N-acetyltransferase 2 (*NAT2*).[164]

Other cancers. Takkouche et al included breast cancer and childhood cancers in their meta-analysis.[153] Efird et al studied the association between the use of hair-coloring agents the month before or during pregnancy with childhood brain tumors in 1218 cases between 1976 and 1994.[165] Heineman et al studied 112 women in Nebraska newly diagnosed with brain cancer (glioma).[166] McCall et al reported on the relationship between childhood neuroblastomas and maternal hair dye use in 538 children born between 1992 and 1994 in the United States and Canada.[167] Bluhm et al reported on personal hair dye use and risks of glioma, meningioma, and acoustic neuroma.[168] Chen et al reported a case-control study of childhood germ cell tumors and exposure to residential chemicals, including prenatal and postnatal maternal hair dye use.[169]

Reproductive and developmental outcomes. Axmon et al compared fertility parameters in a cohort of Swedish hairdressers with matched controls.[170] Hougaard et al examined the risk of infertility among hairdressers in a 5-year follow-up of female hairdressers in Denmark.[171] Zhu et al reported on pregnancy outcomes among female hairdressers in Denmark.[172] Thulstrup and Bonde conducted an in-depth review of 26 human studies of neural tube defects, cleft lip and cleft palate, congenital heart defects, urinary tract defects, and limb defects in which work and exposure status was known.[173]

Other endpoints. Park et al reported an occupational case-control study of neurodegenerative diseases, including Alzheimer's disease, presenile dementia, and motor neuron disease.[174] Cooper et al determined antinuclear antibody titer in individuals in the general population as a function of occupational history and ever/never use of hair dyes.[175]

Hueber-Becker et al reported exposures of hairdressers to oxidative hair dyes (p-phenylenediamine hydrochloride) under controlled conditions, including estimates of systemic exposure.[176] The authors discussed the adequacy of current safety precautions for handling hair dyes by hairdressers and the risk to health posed by the exposures found.

SUMMARY

Ammonium Thioglycolate, Ethanolamine Thioglycolate, Glyceryl Thioglycolate, and Isooctyl Thioglycolate are used in hair care products, predominantly in permanent waving products at concentrations up to 20%. Calcium Thioglycolate, Potassium Thioglycolate, and Sodium Thioglycolate are used in depilatories at concentrations up to 7%. Thioglycolic acid is used in hair care products (up to 11%) and depilatories (up to 5%). Butyl Thioglycolate, Ethyl Thioglycolate, Isopropyl Thioglycolate, Magnesium Thioglycolate, and Methyl Thioglycolate are not currently reported to be used. Noncosmetic uses of Thioglycolic Acid include as a raw material for the synthesis of pharmaceuticals, as a vinyl stabilizer, and as a reagent for iron.

In a test of the effectiveness of glove material as a barrier to Glyceryl Thioglycolate in a typical permanent wave solution, all glove material mounted in a diffusion cell provided a substantial barrier, with latex performing the best. The study demonstrated that penetration increases as a function of time and that all glove material can act as a reservoir of Glyceryl Thioglycolate. A combination of glove material and human skin in vitro mounted in a diffusion cell effectively prevented any penetration to the receptor fluid. Skin alone, rinsed after 10 minutes of application of Glyceryl Thioglycolate, prevented penetration to the receptor fluid.

A 30% to 40% dilution of a 25.0% solution (330 mg/kg) of [^{35}S]Thioglycolic Acid applied to dorsal skin of rabbits was excreted within 5 hours. Mean cutaneous absorption of 11% Ammonium [^{14}C]Thioglycolate at pH 6, pH 7, and pH 8 was 0.27%, 0.24%, and 0.26%, respectively, in rats.

A permanent wave solution containing 11% Glyceryl Thioglycolate applied to human skin in vitro in a diffusion cell, after 8 hours and no rinsing, resulted in 0.036 mg/cm^2 penetration. At 48 hours, the amount with no rinsing was 10.28 mg/cm^2. The amount of [^{14}C]Glyceryl Thioglycolate that

permeated the skin in samples that had been rinsed 10 minutes after application was 0.0002 mg/cm^2 at 8 hours and 0.0005 mg/cm^2 at 48 hours.

After i.v. 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 i.v. with 50 mg/kg of [^{35}S]Thioglycolic Acid. Residual ^{35}S blood concentrations at 0.5 to 7 hours after injection 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 hours after 100 mg/kg of [^{35}S]Thioglycolic Acid was administered to groups of rats via i.v. and i.p. 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 hours after Thioglycolic Acid (100-150 mg/kg) was injected i.p. 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 hours after i.p. injection of a rat with 150 mg/kg of Sodium Thioglycolate.

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 75%, and in a study in which mice were dosed with a 5% solution of Sodium Thioglycolate.

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

Dermal toxicity studies for 10.98% Ammonium Thioglycolate and Glyceryl Thioglycolate indicate that these chemicals were practically nontoxic in rabbits in acute exposures. 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.

In a subchronic study, no significant gross lesions were observed in rats that were injected i.p. with 100 mg/kg of 5.0% Sodium Thioglycolate 5 days per week for 24 weeks.

Transient conjunctival redness was observed in the eyes of 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.

Two in vitro tests using Calcium Thioglycolate (10% and 100%) were used to test for eye irritation. The results at 10% Calcium Thioglycolate correlated to a Draize maximum average score (MAS) of 4.0/110 and a 24-hour total score of 2.7/110. At 100% the results correlated to a Draize MAS of 79.7/110 and a 24-hour average score of 52.3/110, which is considered severe.

A solution of 71% Ammonium Thioglycolate was classified as slightly irritating when applied to intact skin of rabbits for 4 hours (semi-occlusive patches). 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 hours (occlusive patches) and 24 hours (semi-occlusive patches). A 7.0% Ammonium Thioglycolate solution also was classified as a skin irritant after being applied (cotton patches) for 24 hours to abraded and intact skin of rabbits. Calcium Thioglycolate (99.8%) and 98% Sodium Thioglycolate solution were moderately irritating to intact rabbit skin after a 4-hour exposure (semi-occlusive patches), while 83% Ethanolamine Thioglycolate and 43% Potassium Thioglycolate solutions were only slightly irritating under the same test conditions. Glyceryl Thioglycolate (100%) was classified as a severe skin irritant after being applied (occlusive patches) for 24 hours 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. A solution of 99% Thioglycolic Acid in an EpiDerm Skin Model test was corrosive.

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.

No sensitization was observed in guinea pigs exposed to 50% Ammonium Thioglycolate in a Buehler test. 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%). Sensitization occurred in maximization tests for Glyceryl Thioglycolate (67.9%). Results from local lymph node assays indicated that Ammonium Thioglycolate (8% dilution of an unreported concentration), Calcium Thioglycolate (30% dilution of an unreported concentration), Ethanolamine Thioglycolate (25% dilution of 83%), Potassium Thioglycolate (25% dilution of 43%), and Sodium Thioglycolate (10% dilution of 98%) induced sensitization.

Sodium Thioglycolate was topically applied to pregnant New Zealand white rabbits at doses of 10, 15, 25, and 65 mg/kg per day from gestational days 6 to 29. Moderate to severe erythema occurred at doses greater than 15 mg/kg per day; however, fetuses were unaffected and developmental toxicity for rabbits under conditions of this study was greater than 65 mg/kg per day.

In another developmental toxicity study, pregnant Sprague-Dawley rats were topically exposed to Sodium Thioglycolate at doses of 50, 100, and 200 mg/kg per day from gestational days 6 to 19. There was 1 reported maternal death at 200 mg/kg per day. Feed consumption, water consumption, and body weights of the mothers all significantly increased. The body weights of the fetuses were significantly lower than the controls; however, there was no other evidence of embryofetal toxicity. A NOAEL of 100 mg/kg per day was determined for these rats.

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. Glyceryl Thioglycolate was nonclastogenic in human lymphocytes. 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 1.0N 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 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.

Depilatories containing 6.88% Potassium Thioglycolate did not induce skin irritation in subjects in 3 different efficacy studies.

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

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 2 groups of normal subjects (different experimental procedures), mild to moderate skin irritation was observed. In 1 of the 2 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 or 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 RIPTs 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 RIPTs. 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 RIPTs, 10.8%, 18.0%, and 21.6% Glyceryl Thioglycolate did not induce clinically meaningful irritation or 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 2 groups of normal subjects (different experimental procedures), mild to moderate skin irritation was observed in 1 group, and mild to marked skin irritation was observed in the other group. In 1 of the 2 groups, 2 subjects had what was referred to as possible and probable moderate-grade allergic contact dermatitis.

In studies of normal subjects, RIPTs 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 2 acid wave products containing 22.6% Glyceryl Thioglycolate were tested, 1 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 Thioglycolate 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 the 11 patients (8 hairdressers, 3 clients) patch tested with 1.0% Glyceryl Thioglycolate in petrolatum.

Epidemiology studies that consider the possible link between hair dye use and bladder cancer, lymphoma and leukemia, other cancers, reproductive and developmental outcomes, and other endpoints were described.

DISCUSSION

As noted in the introduction, an earlier safety assessment by the CIR Expert Panel addressed the safety of Thioglycolic Acid, its ammonium salt, and glyceryl ester, but did not include other salts and esters. Because the new conclusion represents an amended conclusion for these ingredients, it is considered an amended safety assessment.

Because the molecular weights (MW) of these Thioglycolic Acid derivatives vary considerably, a

common practice is to express the concentration as equivalent levels of Thioglycolic Acid. A concentration of Ammonium Thioglycolate (MW 109.13) of 18% corresponds to a level of Thioglycolic Acid (MW 92.12) of 15.2% (18 × 92.12/109.13). A concentration of Glyceryl Thioglycolate (MW 166.15) of 23.4% corresponds to a level of Thioglycolic Acid of 13% (23.4 × 92.12/166.15).

Substantial new data are discussed below, notably on Sodium Thioglycolate. Based on new in vitro glove penetration data, methods to prevent dermal exposure to hairdressers to thioglycolates are also discussed.

Thioglycolic Acid Esters

In considering the available safety test data on Methyl Thioglycolate, Ethyl Thioglycolate, Isopropyl Thioglycolate, Glyceryl Thioglycolate, and Butyl Thioglycolate, the CIR Expert Panel was concerned with the paucity of data. The only Thioglycolic Acid esters that are currently reported by industry to be in use are Glyceryl Thioglycolate and Isooctyl Thioglycolate, yet the others are described as cosmetic ingredients and presumably could be used. Although data describing the physical and chemical properties of these esters are generally available, information on the manufacturing process and data on impurities are available only for Glyceryl Thioglycolate.

Based on the available data, Thioglycolic Acid esters are not considered to be genotoxic, nor do they present any risk of carcinogenesis.

Studies are included which evaluated the dermal irritation and sensitization potential of Glyceryl Thioglycolate, but not for the other esters. These data demonstrate that concentrations of Glyceryl Thioglycolate used in many cosmetic products can be irritating to the skin and eyes, and that repeated exposures can cause skin sensitization. It is the opinion of the Expert Panel that it is likely that the pattern of skin and eye irritation and skin sensitization seen for the glyceryl ester would also be found for the other esters. If these esters are used (or potentially used) in hair care products, a limitation on use concentration and adequate instructions to hairdressers to avoid skin contact (such as by wearing gloves) and to minimize consumer skin exposure (by limiting the frequency of product use) would be adequate to assure that irritation and sensitization are not a concern.

The CIR Expert Panel considered the skin penetration potential of Glyceryl Thioglycolate in a study that investigated protective glove materials. Penetration through unprotected skin was 36 $\mu g/cm^2$ over 8 hours from a Glyceryl Thioglycolate solution with 11% equivalent free Thioglycolic Acid. If the skin was rinsed after 10 minutes, penetration was 0.20 $\mu g/cm^2$ over 8 hours. These data suggested low dermal penetration. While skin penetration data are lacking for the other Thioglycolate esters, such esters would be hydrolyzed into their constituent part in the presence of water, and the CIR Expert Panel believes that the absorption potential of Glyceryl Thioglycolate can be extrapolated to the other esters.

Thioglycolic Acid Salts

The CIR Expert Panel noted that the calcium, potassium, and sodium salts are reported to be used in depilatories, while the ammonium and ethanolamine salts are used in hair care products. Because ionic compounds, such as these Thioglycolic Acid salts, normally dissociate into their constituent ions when they dissolve in water, it would be expected that this would occur in any cosmetic formulation that is water based. In toxicity studies, therefore, data from 1 salt could be extrapolated to the others.

The available acute, subchronic, and chronic toxicity data, primarily for Ammonium Thioglycolate and Sodium Thioglycolate, demonstrate little toxicity. In a dermal reproductive and developmental toxicity study using Sodium Thioglycolate, for example, adverse effects were limited to body weight changes, and a no-adverse-effect level of 100 mg/kg per day was determined, suggesting to the CIR Expert Panel that these salts are not significant reproductive or developmental toxins. In carcinogenicity studies of mice and rabbits, no compound related adverse effects of Sodium Thioglycolate were seen, again suggesting the absence of a safety concern.

Thioglycolic Acid salts can be irritating to the skin and eyes, and repeated exposures can cause skin sensitization. Without adequate skin protection, the CIR Expert Panel noted that repeated applications of cosmetic products containing Ammonium Thioglycolate by hairdressers to multiple clients over a period of time should be avoided. As above, the CIR Expert Panel considered that hairdressers should avoid skin contact and minimize consumer skin exposure.

The CIR Expert Panel further discussed skin irritation and sensitization with specific reference to the use of Thioglycolic Acid salts in depilatories. The

CIR Expert Panel recognizes that nearly all methods of hair removal cause some degree of irritation. In the experience of the CIR Expert Panel, although these chemicals have the potential to be severely irritating to the skin, clinically significant adverse reactions to these ingredients used in depilatories are not commonly seen. This suggests that current products are formulated to be practically nonirritating under conditions of recommended use. Formulators should take steps necessary to assure that current practices are followed. Based on this evaluation, the CIR Expert Panel has added language to the conclusion that specifically notes that Thioglycolic Acid salts in depilatories are safe when formulated to be nonirritating under conditions of recommended use. The CIR Expert Panel recognizes that this new language represents an amendment to the previous conclusion for Ammonium Thioglycolate.

Because Ethanolamine Thioglycolate may dissociate in use, the CIR Expert Panel considered its earlier finding that Monoethanolamine (also known as Ethanolamine) should be used only in rinse-off products is a restriction that also should be applied to Ethanolamine Thioglycolate. In practice, uses of Ethanolamine Thioglycolate were limited to rinse-off products, consistent with this restriction.

Thioglycolic Acid

While there are limited data on Thioglycolic Acid itself, the available data show the same pattern of effects as the salts. Therefore, the Expert Panel considered that the available data on the toxicity of Thioglycolic Acid salts could be extended to support the safety of Thioglycolic Acid as used in both hair care products and depilatories. The CIR Expert Panel recognizes that the new language regarding depilatory use, as discussed above, represents an amendment to the previous conclusion for Thioglycolic Acid.

Hairdresser Skin Protection

The CIR Expert Panel discussed the need for adequate skin protection for hairdressers in its original safety assessment and has repeated it above. Whereas only 1 study is currently available, the CIR Expert Panel notes that this study demonstrates a variation in the relative permeability of protective glove materials. While all gloves provide a measure of protection, PVC and latex gloves appear to be more protective than vinyl or nitrile gloves. The study also found that glove material may act as a reservoir for Glyceryl Thioglycolate, suggesting that protective gloves should not be reused. Direct application of Glyceryl Thioglycolate to the skin followed by a water rinse after 10 minutes was as effective in preventing skin absorption as was glove use. The CIR Expert Panel suggests that hairdressers follow a procedure of glove use, followed by removal and disposal of the glove without reuse, followed by rinsing their hands and forearms in water.

Heavy Metals

The CIR Expert Panel expressed concern about toxic metal residues that may be present in Thioglycolic Acid and its salts and esters and advised industry that these ingredients should not contain more than: 3 mg/kg of arsenic (as As), 1 ppm mercury (as Hg), and 0.1 mg/kg of lead (as Pb). The Panel recognizes that these limits were developed for uses other than cosmetics, but considers that such limits would assure that any cosmetic product with these ingredients can be used safely.

Hair Dye Epidemiology

In considering hair dye epidemiology data, the CIR Expert Panel concluded that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other endpoints.

CONCLUSION

Based on the available data, the CIR Expert Panel concluded that Ammonium Thioglycolate*, Butyl Thioglycolate, Calcium Thioglycolate, Ethanolamine Thioglycolate, Ethyl Thioglycolate, Glyceryl Thioglycolate*, Isooctyl Thioglycolate, Isopropyl Thioglycolate, Magnesium Thioglycolate, Methyl Thioglycolate, Potassium Thioglycolate, Sodium Thioglycolate, and Thioglycolic Acid* are safe for use in hair straighteners, permanent waves, tonics, dressings, and so forth, wave sets, other noncoloring hair products, and hair dyes and colors, as described in this safety assessment, at concentrations up to 15.2% (as Thioglycolic Acid). Hairdressers should avoid skin contact and minimize consumer skin exposure. Calcium Thioglycolate, Potassium Thioglycolate, Sodium Thioglycolate, and Thioglycolic Acid in depilatories are safe when formulated to be nonirritating under conditions of recommended use.

Note

* This represents an amended conclusion for Ammonium Thioglycolate, Thioglycolic Acid, and Glyceryl Thioglycolate.

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