SUMMARY OF DATA FOR CHEMICAL SELECTION

THIOGLYCOLIC ACID, SALTS AND ESTERS

68-11-1, 367-51-1, 814-71-1, 5421-46-5, 30618-84-9

BASIS OF NOMINATION TO THE CSWG

The nomination of thioglycolic acid to the CSWG is based on very high production volume, extensive exposure potential, and lack of information on potential carcinogenicity. Dr. Elizabeth Weisburger, a member of the American Conference of Governmental Industrial Hygienists (ACGIH) TLV Committee as well as the Chemical Selection Working Group (CSWG), provided a list of 281 chemical substances with ACGIH recommended TLVs for which there were no long-term studies cited in the supporting data and no designations with respect to carcinogenicity. She presented the list to the Chemical Selection Planning Group (CSPG) for evaluation as chemicals which may warrant chronic testing; it was affirmed at the CSPG meeting held on August 9, 1994, that the 281 "TLV Chemicals" be reviewed as a Class Study. As a result of the class study review, thioglycolic acid is presented as a candidate for testing by the National Toxicology Program because of:

- potential for broad consumer exposures based on cosmetic use
- potential for occupational exposures based on high production volume
- evidence of occupational exposures based on TLV and other literature documentation
- lack of chronic toxicity data.

Sources of human exposure to thioglycolic acid are both occupational and general (consumer); and the exposure potential is considered high based on cosmetic use and an estimated U.S. annual production volume range of 2.6 to 11.5 million pounds for thioglycolic acid, an estimate of 30,055 worker exposures (15,142 female) reported in the NOES database for thioglycolic acid, 41,132 worker exposures (30,869 female) for ammonium thioglycolate, and 7,553 worker exposures (6,204 female) for sodium thioglycolate.

Genetic toxicity test results include negative Ames *Salmonella* assays for thioglycolic acid, the ammonium and sodium salts and the glyceryl monoester; a negative *E. coli* assay for the acid; a negative result in a mouse micronucleus assay for the sodium salt; and negative results in a fly species for sex-linked recessive mutations for the acid and the sodium salt. The overall negative results in a limited number of short-term assays for mutagenicity combined

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with a lack of 2-year mammalian bioassay data suggest a low or unknown suspicion of carcinogenicity for thioglycolic acid.

SELECTION STATUS

ACTION BY CSWG: 12/6/95

Studies Requested: Reproductive studies for sodium thioglycolate

Priority: High

Rationale/Remarks:

- Widespread worker and consumer exposure
- Exposure is mainly to the female population
- Used mainly in cosmetic products, permanent wave and hair straightening products
- Recommend that Dr. Sheila Zahm (NCI) include the thioglycolates in the NCI study on hair dyes

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY: Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee, was contacted at the Environmental Protection Agency (EPA) for information on the total annual production level of thioglycolic acid. Dr. Walker reported it to be within a range of 2.6 to 11.5 million pounds for 1989 (Walker, 1995a). He also provided a summary of actions of the TSCA ITC on this chemical (see Regulatory Status section).

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CHEMICAL IDENTIFICATION

Structural class: Thiol carboxylic acid, salts, and ester

CAS Registry Number: 68-11-1

Chemical Abstract Name: Acetic acid, mercapto- (9CI, 8CI)

Synonyms: Mercaptoacetate; mercaptoacetic acid; α-mercaptoacetic acid; 2-mercaptoacetic acid; 2-mercaptoethanoic acid; sulfhydrylacetic acid; thioglycolic acid; 2-thioglycolic acid; thioglycolic acid; thiovanic acid

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CAS Registry Number: 367-51-1

Chemical Abstract Name: Acetic acid, mercapto-, monosodium salt (9CI, 8CI)

Synonyms and Trade Names: Mollescal SF; sodium thioglycolate; mercaptoacetic acid, sodium salt; monosodium mercaptoacetate; sodium mercap-toacetate; thioglycolic acid, sodium salt; USAF EK-5199; CTFA 02954; Erhavit D

CAS Registry Number: 814-71-1

Chemical Abstract Name: Acetic acid, mercapto-, calcium salt (2:1) (9CI, 8CI)

Synonyms and Trade Names: Calcium mercaptoacetate; calcium thioglycolate; thioglycolic acid, calcium salt; CTFA 00404; DEPIL; Ebacream; JULLY; Surgex; VIKOR

CAS Registry Number: 5421-46-5

Chemical Abstract Name: Acetic acid, mercapto-, monoammonium salt (9CI, 8CI)

Synonyms and Trade Names: Ammonium mercaptoacetate; ammonium thioglycolate; ammonium thioglycolate; Thiofaco A-0; thioglycolic acid, ammonium salt

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CAS Registry Number: 30618-84-9

Chemical Abstract Name: Acetic acid, mercapto-, monoester with 1,2,3-propanetriol (9CI)
Acetic acid, mercapto, monoester with glycerol (8CI)

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Synonyms: Acetic acid, mercapto-, ester with glycerol; glycerin monothioglycolate; glycerol monomercaptoacetate; glyceryl monothioglycolate

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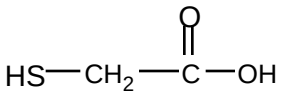
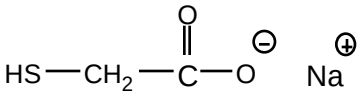
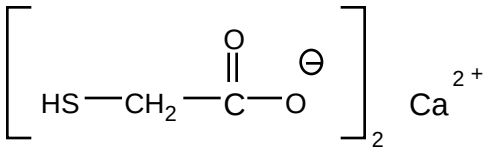
Structures, Molecular Formulae and Molecular Weights:



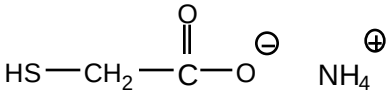
$C_2H_4O_2S$ (thioglycolic acid)



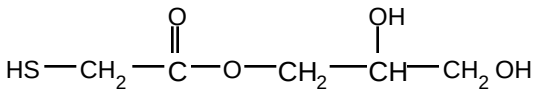
$C_2H_3O_2S.Na$ (sodium thioglycolate)



$C_4H_6O_4S_2.Ca$ (calcium thioglycolate)



$C_2H_3O_2S.H_4N$ (ammonium thioglycolate)
Mol. wt.: 109.15



$C_5H_{10}O_4S$ (glyceryl monothioglycolate)

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Chemical and Physical Properties

Thioglycolic Acid

Description:	Colorless liquid with unpleasant odor characteristic of the sulfhydryl group (ACGIH, 1993)
Boiling Point:	120°C at 20 mm Hg (Lide, 1995)
Melting Point:	-16.5°C (Lide, 1995)
Density:	1.325 g/cm^3 at 20°C (Lide, 1995)
Solubility:	Miscible with water, ethanol, ethyl ether, and other organic solvents, slightly soluble in chloroform (Lide, 1995; ACGIH, 1993)
Vapor Pressure:	10 mm Hg at 18°C (ACGIH, 1993)
Reactivity:	Combustible (Lewis, 1993); readily oxidized by air (Budavari, 1989); reacts with molecular oxygen to form dithiodiglycolic acid; reacts with diethyl acetylmalonate to form acetylmercaptoacetic acid and diethyl malonate (CTFA, 1991)

Sodium Thioglycolate (from Lewis, 1993)

Description:	Hygroscopic crystals with a characteristic odor
Solubility:	Soluble in water, slightly soluble in ethanol
Reactivity:	Combustible; discolors on exposure to air or iron

Calcium Thioglycolate (from Budavari, 1989; Lewis, 1993)

Description:	White powder; trihydrate: prismatic rod crystals, odorless or faint mercaptan odor, somewhat astringent and fetid taste
Melting Point:	Decomposes at 250°C
Solubility:	Soluble in water, very slightly soluble in alcohol and chloroform, practically insoluble in diethyl ether, petroleum ether, and benzene

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Ammonium Thioglycolate (from CTFA, 1991)

Description:	Slightly pink aqueous solution with a repulsive odor
Solubility:	Miscible in water and ethanol
Reactivity:	Oxidized in air to disulfide salts

Glyceryl Monothioglycolate (from CTFA, 1991)

Description:	Colorless liquid with an odor typical of esters
Boiling Point:	300°C
Specific Gravity:	1.32
Solubility:	Miscible with water
Reactivity:	Oxidized in air

Technical Products and Impurities: ***Thioglycolic Acid.*** Thioglycolic acid is commercially available in bulk quantities (tank truck, 55-gallon drum, and 5-gallon pail) from Elf Atochem North America, Inc., and Evans Chemetics/Hampshire Chemical Corp. It is also available as reagent grade in research quantities from Spectrum Chemical Mfg. Corp. (Kuney, 1994) and at 97% purity from Aldrich Chemical Co. (1994).

A thioglycolic acid commercial product was reported to consist of thioglycolic acid (78% min.), iron (0.02 ppm max.), and monochloroacetic acid (0.05% max.). The following are listed in a safety assessment by the CTFA as product specifications with regard to impurities in thioglycolic acid: dithiodiglycolic acid (2.0% max.), sulfated ash (0.05% max.), arsenic (3 ppm max.), copper (1 ppm max.), and lead (20 ppm max.) (CTFA, 1991).

Sodium Thioglycolate. 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% max.; K, 0.01% max.; Ca, Mg, 0.005% max.; Al, Ba, Bi, Cd, Co, Cr, Cu, Fe, Li, Mn, Mo, Ni, Pb, Sr, Zn, 0.0005% max. (Fluka Chemical Corp., 1995). It is also available from Aldrich Chemical Co. at 97% purity (Aldrich Chemical Co., 1994).

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Calcium Thioglycolate. Calcium thioglycolate (trihydrate) is commercially available in research quantities with purities ranging from 98% to greater than 99% with the following impurities: chloride, 0.05% max.; sulfate, 0.005% max; Sr, 0.01% max.; Na, 0.05% max.; K, 0.005% max.; Ba, Bi, Cd, Co, Cr, Cu, Fe, Li, Mn, Mo, Ni, Pb, Zn, 0.0005% max. (Fluka Chemical Corp., 1995).

Ammonium Thioglycolate. Ammonium thioglycolate is commercially available in bulk quantities (tank car, tank truck, and/or 55-gallon drum) from Evans Chemetics/Hampshire Chemical Corp. and Witco Corp. Witco Corp. also offers ammonium thioglycolate in cosmetic and industrial grades. Gallard-Schlesinger Industries, Inc. offers a 60% cosmetic grade (Kuney, 1994).

An ammonium thioglycolate commercial product was reported to have an ammonium thioglycolate level of 60% with a maximum dithiodiglycolate content of 2%. The following are listed in a safety assessment by the CTFA as product specifications with regard to impurities in ammonium thioglycolate: ammonium thioglycolate (50-60%), sulfated ash (0.05% max.), arsenic (3 ppm max.), iron (1 ppm max.), and lead (20 ppm max.) (CTFA, 1991).

Glyceryl Monothioglycolate. A glyceryl monothioglycolate commercial product was reported to consist of glyceryl thioglycolate (80%) and thioglycolic acid (2% max.), as well as glycerin and traces of dithioglycolate species (CTFA, 1991).

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EXPOSURE INFORMATION

Production and Producers:

Thioglycolic Acid. Thioglycolic acid can be prepared by (1) reacting sodium sulfhydrate with sodium chloroacetate; (2) electrolysis of dithioglycolic acid (from sodium sulfide and sodium chloroacetate); and (3) heating chloroacetic acid with potassium hydrogen sulfide (Budavari, 1989; Lewis, 1993). A Chinese study reported that thioglycolic acid can be produced by the Bunte salt method using sodium thiosulfate and sodium chloroacetate as major raw materials (Peng *et al*., 1994).

The annual production of thioglycolic acid was reported to be in the range of 2,624,322 to 11,555,360 lbs based on non-confidential data received by the EPA for 1989 (Walker, 1995a). No other quantitative information on annual production was found in the available literature. However, thioglycolic acid is listed in the U.S. International Trade Commission (USITC) publication, *Synthetic Organic Chemicals, US Production and Sales*. Evans Chemetics has been listed as a manufacturer of thioglycolic acid from 1957 to 1993. Other manufacturers listed include Rayette, Inc. from 1957 to 1961; Halby Products Co., Inc. from 1961 to 1972; Akzo Chemicals, Inc. in 1979; and Elco Corp., Sub. of Dextrex Chemical Industries, Inc. in 1988. No production or sales quantities were included to avoid disclosure of individual company operations, indicating a quantity ≥ 4,500 kg (10,000 lbs) or sales ≥ $10,000 (USTC, 1958, 1959, 1962, 1969, 1974; USITC, 1977-1992, 1994a,b).

Thioglycolic acid is listed in the EPA's TSCA Inventory (STN International, 1995a).

Thioglycolic acid is reportedly produced and/or distributed in the United States by the following chemical companies, according to recent issues of chemical industry directories (Chemical Information Services, Inc., 1994; Hunter, 1994; Kuney, 1994; Van, 1994).

AC Industries, Inc., Sattva Chemical Co. Div.
Alemark Chemicals
Allchem Industries, Inc.
Amber Synthetics Amsyn Inc.
Chugai Boyeki (America) Corp.
Elf Atochem North America, Inc.
Evans Chemetics/Hampshire Chemical Corp.
Kaltron/Pettibone
Maypro Industries, Inc.
Spectrum Chemical Mfg. Corp.
Witco Corp.

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Sodium Thioglycolate. Sodium thioglycolate is listed in the USITC publication *Synthetic Organic Chemicals, US Production and Sales*. Evans Chemetics has been listed as a manufacturer from 1957 to 1992. Other manufacturers include Medical Chemicals Corp. in 1967 and an undisclosed company from 1982 to 1988. Thioglycolic acid salts were not listed individually but as a group in 1993; however, the reporting company was not disclosed. No production or sales quantities were included to avoid disclosure of individual company operations, indicating a quantity ≥ 4,500 kg (10,000 lbs) or sales ≥ $10,000 (USTC, 1958, 1959, 1962, 1969, 1974; USITC, 1977-1992, 1994a,b).

Sodium thioglycolate is listed in the EPA's TSCA Inventory (STN International, 1995a).

Sodium thioglycolate is reportedly produced and/or distributed in the United States by Evans Chemetics/Hampshire Chemical Corp. and Spectrum Chemical Manufacturing Corp., according to recent chemical industry directories (Chemical Information Services, Inc., 1994; Hunter, 1994; Van, 1994).

Calcium Thioglycolate. Calcium thioglycolate is listed in the USITC publication, *Synthetic Organic Chemicals, US Production and Sales*. Evans Chemetics has been listed as the manufacturer from 1957 to 1988. Thioglycolic acid salts were not listed individually but as a group in 1993; however, the reporting company was not disclosed. No production or sales quantities were included to avoid disclosure of individual company operations, indicating a quantity ≥ 4,500 kg (10,000 lbs) or sales ≥ $10,000 (USTC, 1958, 1959, 1962, 1969, 1974; USITC, 1977-1989, 1994b).

Calcium thioglycolate is listed in the EPA's TSCA Inventory (STN International, 1995a).

Ammonium Thioglycolate. Ammonium thioglycolate can be prepared by reacting thioglycolic acid with aqueous ammonia (CTFA, 1991).

Ammonium thioglycolate is listed in the USITC publication *Synthetic Organic Chemicals, US Production and Sales*. Evans Chemetics has been listed as a manufacturer from 1957 to 1991. Other listed manufacturers include Halby Products Co., Inc. from 1957 to 1972; Summit Chemical Products Corp. in 1957 and 1958; Helene Curtis Industries, Inc. in 1957

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and 1958; Morton Chemical Co. in 1957 and 1958; Gillette Chemical Co., Division of Gillette Co. from 1967 to 1975; Witco Chemical Corp. from 1986 to 1992; and C.N.C. International, Inc. in 1992. Thioglycolic acid salts were not listed individually but as a group in 1993; however, the reporting company was not disclosed. No production or sales quantities were included to avoid disclosure of individual company operations, indicating a quantity ≥ 4,500 kg (10,000 lbs) or sales ≥ $10,000 (USTC, 1958, 1959, 1962, 1969, 1974; USITC, 1977-1992, 1994a,b).

Ammonium thioglycolate is listed in the EPA's TSCA Inventory (STN International, 1995a).

Ammonium thioglycolate is reportedly produced and/or distributed in the United States by the following chemical companies, according to recent issues of chemical industry directories (Chemical Information Services, Inc., 1994; Hunter, 1994; Kuney, 1994; Van, 1994).

Allchem Industries, Inc.
Evans Chemetics/Hampshire Chemical Corp.
Gallard-Schlesinger Industries, Inc.
Kaltron/Pettibone
Tomen (America) Inc.
Witco Corp.

Glyceryl Monothioglycolate. Glyceryl monothioglycolate is prepared via esterification of a mixture of glycerin and thioglycolic acid. The result is a complex mixture of the alpha and beta monoester, diesters, and triester. Unreacted thioglycolic acid, water, glycerin, and dithioglycolate species, from oxidation of the thiol reactant and products, also are present (CTFA, 1991).

Glyceryl monothioglycolate is listed in the USITC publication *Synthetic Organic Chemicals, US Production and Sales, 1992*. The manufacturer listed is Evans Chemetics. Thioglycolic acid salts were not listed individually but as a group in 1993; however, the reporting company was not disclosed. No production or sales quantities were included to avoid disclosure of individual company operations, indicating a quantity ≥ 4,500 kg (10,000 lbs) or sales ≥ $10,000 (USITC, 1994a,b).

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Glyceryl monothioglycolate is listed in the EPA's TSCA Inventory (STN International, 1995a).

Glyceryl monothioglycolate is reportedly produced and/or distributed in the United States by the following chemical companies, according to a recent chemical industry directory (Davis, 1985; Chemical Information Services, Inc., 1994).

Evans Chemetics/Hampshire Chemical Corp.
Gallard-Schlesinger Corp.
Pfaltz & Bauer, Inc.
Witco Chemical Corp.

Use Pattern: Thioglycolic acid, its salts and glyceryl esters are used in cosmetic hair-care products. Thioglycolates reduce the cystine disulfide linkages in the hair cortex, thereby weakening the keratin molecule. Cosmetic products containing thioglycolic acid, ammonium thioglycolate, and glyceryl thioglycolates are applied commonly to the face, legs, and hair and may come in contact with the scalp and ocular and nasal mucosae. The predominant use of thioglycolic acid, ammonium thioglycolate, and glyceryl thioglycolates is in permanent waving products. Use concentrations of these ingredients are as follows: thioglycolic acid, > 0.1-50.0%; ammonium thioglycolate, > 0.1-50.0%; and glyceryl thioglycolate, > 1.0-50.0% (CTFA, 1991). Thioglycolic acid, sodium thioglycolate, and calcium thioglycolate are reportedly used as depilatories in addition to use in hair-waving preparations. The minimum active concentration of thioglycolic acid and calcium thioglycolate in depilatories is reported to be 5% and 7%, respectively (NLM, 1995a). In addition, thioglycolic acid is used as an organic chemical and pharmaceutical intermediate, a vinyl stabilizer, and an analytical reagent; the sodium salt is used as an analytical reagent and in bacteriology for the preparation of thioglycolate media; and the calcium salt is used in leather tanning (Budavari, 1989, CTFA, 1991).

Thioglycolic Acid. Thioglycolic acid functions as an antioxidant, depilating agent, hair waving/straightening agent, and reducing agent. As an antioxidant useful in cosmetics, thioglycolic acid is intended to protect the product but not the skin against oxidative damage resulting from ultraviolet radiation or singlet oxygen formation, according to Rieger, (1993). Reported cosmetic uses include content in permanent waves, hair dyes and colors, hair straighteners, miscellaneous hair products, and depilatories, often in

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combination with any one of its derivatives, usually in the form of the ammonium, sodium, or calcium salt. In cosmetics, it is always present as an anion ($HSCH_2COO^-$ or $^-SCH_2COO^-$). The active species in the process of hair waving is the dianion. Noncosmetic uses of thioglycolic acid include use in the manufacture of pharmaceuticals and thioglycolates, as a vinyl stabilizer, and as an analytical reagent for iron, molybdenum, silver, and tin (Nikitakis, 1988; Budavari, 1989; ACGIH, 1993; CTFA, 1991; Lewis, 1993; Kuney, 1994).

Recent studies and patents cited in *Chemical Abstracts* on the use of thioglycolic acid include the following (STN International, 1995b).

Cosmetic

- US patents: in hair permanent wave-setting compositions (Nandagiri *et al*., 1994)
- French patents: as a component of deodorant products for waving hair (Bauer *et al*., 1995)
- Japanese patents: as a hair straightening agent (Tabata *et al*., 1995) and in hair dye preparations (Sugimoto, 1995)
- German patents: in hair wave-setting preparations (Hartmann, 1994; Maresch & Burg, 1994; Tennigkeit, 1994)

Noncosmetic

- US study: for the preparation of technetium oxomercaptoacetylglcylglycylglycine and mercaptoacetylglycylglycylglycinate ester complexes useful in nuclear medicine (Grummon *et al*., 1995)
- Australian study: for the suppression of iron interference in a method for the determination of boron in soil extracts, plant material digests, and concentrated HCl digests using the azomethine-H procedure (Zarcinas, 1995)
- Chinese studies: as a releasing agent in the determination of tin with selective chelatometric titration (Wang & Li, 1994); in the preparation of a new kind of foam plastic loaded with sulfhydryl carbon powder made for the separation and concentration of palladium (Long & Li, 1994)
- Japanese patents: as a surface modifier for ultrafine feather powders to improve their oil or human sweat absorption and water retention (Kawaguchi, 1994); as an agent for opening disulfide bonds in the manufacture of polyolefin fibers containing protein-type fine powders with natural feeling (Okuya *et al*., 1994)

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- Spanish patent: in the preparation of fluorescent acrylic polymer aqueous solutions (Contijoch Mestres, 1994)

Sodium Thioglycolate. Sodium thioglycolate functions as an antioxidant, depilating agent, hair waving/straightening agent, and reducing agent. Its primary cosmetic use is in depilatories. Its use in cold-waving of hair, in bacteriology for the preparation of thioglycolate media, and as an analytical reagent has also been reported (Nikitakis, 1988; Budavari, 1989; Lewis, 1993).

Calcium Thioglycolate. Calcium thioglycolate is used in depilatories and hair-waving preparations as well as in tanning leather and in wool shearing (Nikitakis, 1988; Budavari, 1989; Lewis, 1993; NLM, 1995a).

Ammonium Thioglycolate. Ammonium thioglycolate functions as a depilating agent, hair waving/straightening agent, and reducing agent (Nikitakis, 1988). It is commonly used in permanent wave and hair straightening products and may be used in permanent hair colors (as an anti-oxidant) at levels up to 0.25% (Budavari, 1989; CTFA, 1991). Other reported cosmetic uses of ammonium thioglycolate include in miscellaneous hair-care products (Nikitakis, 1988). Recent studies and patents cited in *Chemical Abstracts* on the use of ammonium thioglycolate as a hair preparation ingredient include the following (STN International, 1995b).

- US patents: in hair permanent waving compositions (Clifton & Cade, 1994; Nandagiri *et al*., 1994; Burmeister, 1995)
- German patents: in hair wave-setting preparations (Maresch & Burg, 1994; Tennigkeit, 1994)
- Japanese patents: in hair wave-setting, hair straightening, and hair dye preparations (Ookura & Yamakawa, 1994; Segawa & Ayano, 1994; Nakamura, 1995; Sugimoto, 1995; Tabata *et al*., 1995)

Glyceryl Monothioglycolate. Glyceryl thioglycolate esters are used in permanent wave and hair straightening preparations. The monoester is present in cosmetics in the form of either the anion (G-OCO-CH_2S^-) or the non-dissociated compound (G-OCO-CH_2-SH) (Nikitakis, 1988; CTFA, 1991). Recent studies and patents cited in *Chemical Abstracts* on the use of glyceryl thioglycolate esters include the following (STN International, 1995b).

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- US and German patents: in hair permanent waving compositions (Baer & Goldberg, 1978,1979; Tennigkeit & Rose, 1991; Hartmann, 1994; Burmeister, 1995)
- U.S. patent: in the manufacture of nonoxidative permanent dye gels for hair and synthetic fibers (Schultz & Wong, 1994)

Human Exposure: The primary concern for human exposure to thioglycolic acid, sodium thioglycolate, calcium thioglycolate, ammonium thioglycolate, and glyceryl thioglycolate esters is through their use in cosmetics, particularly permanent wave, hair straightening and hair color preparations, and depilatories.

Products containing thioglycolic acid and its salts and esters are commonly applied to the face, legs, and hair, and may come in contact with the scalp and ocular and nasal mucosae. Cold- wave products containing ammonium thioglycolate may be expected to remain on the skin or hair for as long as 10 to 40 minutes. Although permanent waves generally will process in 30 minutes, in actual practice, they may remain on the head for up to 1 hour (CTFA, 1991).

The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 30,055 workers, including 15,142 female employees, were potentially exposed to thioglycolic acid in the workplace; that 41,132 workers, including 30,869 female employees, were potentially exposed to ammonium thioglycolate in the workplace; and that 7,553 workers, including 6,204 female employees, were potentially exposed to sodium thioglycolate in the workplace. The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein (NIOSH, 1990).

A safety assessment by the CTFA (1991) of thioglycolic acid, ammonium thioglycolate, and glyceryl monothioglycolate cautioned that without adequate skin protection, repeated applications of cosmetic products containing the ammonium salt or glyceryl ester by hairdressers to multiple clients over a period of time should be avoided and that hairdressers should avoid skin contact and minimize consumer skin exposure.

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Environmental Occurrence: Thioglycolic acid and its salts and glyceryl esters are not known to occur naturally. No information was found in the available literature identifying these chemicals in environmental media.

Regulatory Status: The ACGIH-recommended threshold limit value-time weighted average (TLV-TWA) for thioglycolic acid is 1 ppm (3.8 mg/m^3) with a notation for skin being a potential significant exposure route. The short-term exposure limit (STEL) has not been established (ACGIH, 1994). The NIOSH-recommended exposure limit for thioglycolic acid is 1 ppm (4 mg/m^3) also with a skin notation, averaged over a 10-hour work shift (NIOSH, 1992).

The following actions have been taken by the TSCA Interagency Testing Committee (ITC) on thioglycolic acid (Walker, 1995b).

- A dossier (IR-114) was completed in January, 1980.
- Thioglycolic acid was deferred (8/10/80) for health and environmental effects testing because available toxicity data suggest that the chemical does not present unreasonable risk to humans; likely environmental effects were minimal; uptake by aquatic organisms, which might yield olfactory problems in edible fish from mercaptan formation, were deemed minor.

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiology studies or case reports investigating the association of exposure to thioglycolic acid, its ammonium, calcium or sodium salts, or its glyceryl esters and cancer risk in humans were identified in the available literature. The ACGIH (1993) reviewed the available literature in their publication *Documentation of the Threshold Limit Values and Biological Exposure Indices*, and reported the following.

- Ocular exposure to dilute solutions of low-molecular-weight organic acids cause conjunctival hyperemia, prompt pain, and corneal injury.
- Ingestion can produce spontaneous hemorrhaging, intravascular coagulation, gastrointestinal damage, and esophageal and pyloric stricture.
- Skin irritation occasionally occurs in professional hair dressers who may be exposed to thioglycolate-containing products, but dermal toxicity is apparently relatively rare in home use.

In a safety assessment by the CTFA (1991) the reported human toxicity of thioglycolic acid and two of its salts was summarized as follows.

Thioglycolic Acid

- A lotion base containing 4.5% thioglycolic acid did not induce skin irritation in any of the patients tested when applied for 10 minutes.

Ammonium Thioglycolate

- The irritant capacity of ammonium thioglycolate solutions depends on the concentration (>7%) of reagent, length of exposure, and formulation/basicity of solution (e.g., cold wave formulations are more irritating). Single applications of 1.0 N and 1.5 N ammonium thioglycolate (approximately 11.0% and 16.5% thioglycolate) in a 48 hour patch test induced skin irritation in less than 10% of subjects tested. Ammonium thioglycolate at concentrations less than 7% (pH 9.6) was not an irritant when applied during a 24 hour patch test, and much longer exposures to 6.5% ammonium thioglycolate (applied daily for 40-60 minutes, over a period of 2 months) also did not induce skin irritation in normal subjects. However, repeated applications (24 hours daily for 21 days) of permanent wave solutions containing 7.1% ammonium thioglycolate, 5.0% urea, and 1.0% ammonium hydroxide caused strong skin irritation reactions in normal subjects.
- Sensitization reactions are most common in subjects with cutaneous disturbances, or a history of use of cold-wave formulas (i.e., in hair dressers). Ammonium thioglycolate (6.0%) was classified as a skin irritant and sensitizer after single applications were made

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to subjects with a history of dermatitis, cutaneous disturbances, and/or a history of use of cold-wave formulations. The sensitizing activity of ammonium thioglycolate is much lower in normal subjects, who display weak sensitization reactions with repeated exposures to greater concentrations of reagent. For instance, repeated application (3 x weekly for 3 weeks) of 18.0% ammonium thioglycolate induced mild to moderate skin irritation in 27% to 47% of normal populations tested, with probable allergic contact dermatitis observed in only one subject.

Glyceryl Monothioglycolate

- The irritant capacity of glyceryl monothioglycolate solutions is greater than that of ammonium thioglycolate solutions. A 21 day skin irritation test of a 2.0% aqueous solution of glyceryl monothioglycolate induced skin irritation in all subjects tested. A challenge application 10 days following completion of the test reportedly induced an allergic response in some of these subjects. Single application of permanent wave solutions containing < 15.4% glyceryl monothioglycolate in a 48 hour patch test was nonirritating to normal subjects, but repeated applications (3 x weekly for 3 weeks) of solutions of glyceryl monothioglycolate of greater concentration (i.e., 23.4%) induced mild to marked skin irritation in up to 1/3 of the test populations (normal subjects), with minimal evidence of sensitization. In other repeated insult patch (semi-occlusive) tests, solutions of 10.8%, 18.0%, and 21.6% glyceryl monothioglycolate did not induce clinically meaningful irritation nor any evidence of induced allergic contact dermatitis in normal subjects. Application of 2.0% and 4.0% solutions of glyceryl monothioglycolate (in petrolatum or water) under an occlusive patch induced mild to intense erythema with edema in normal subjects in repeated insult patch tests with no evidence of sensitization.

- Minimal sensitization was observed in normal subjects treated repeatedly with acid wave products containing glyceryl monothioglycolate. Reactions ranging from no irritation or sensitization to intense erythema (induction and challenge) were observed in subjects patch tested with acid wave products containing up to 22.6% glyceryl monothioglycolate, with no induction of allergic contact dermatitis. Two other acid wave products containing 22.6% glyceryl monothioglycolate were tested; dilutions of these formulations induced reactions that were classified as sensitization and/or cumulative irritation.

- On the other hand, skin sensitization and allergic contact dermatitis was widely observed in patients (hairdressers and clients with cosmetic-related dermatitis) who received single applications of 0.25% to 2.5% glyceryl monothioglycolate in a 48 hour patch test. In contrast, only 1/45 control subjects tested with 2.5% glyceryl monothioglycolate exhibited irritation. Sensitization reactions were also observed in all of the 11 patients (8 hairdressers, 3 clients) patch tested with 1.0% glyceryl monothioglycolate in petrolatum.

Animal Data: Acute toxicity values reported in RTECS for thioglycolic acid, its sodium, calcium, and ammonium salts, and glyceryl monoester are presented in Table 1.

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Table 1. Acute toxicity values reported in RTECS for thioglycolic acid and its salts

Study Type	Thioglycolic Acid	Sodium Thioglycolate	Calcium Thioglycolate	Ammonium Thioglycolate	Glyceryl Monothioglycolate
Oral, LD_{50}	rat: 114 mg/kg mouse: 242 mg/kg rabbit: 119 mg/kg guinea pig: 126 mg/kg mammal: 250 mg/kg	mouse: 504 mg/kg	ND		ND
Skin, LD_{50}	mouse: 47 mg/kg		ND		ND
Skin, LD_{lo}	rabbit: 300 mg/kg		ND		ND
Subcutaneous, LD_{50}		mouse: 293 mg/kg	ND		ND
Inhalation, LC_{lo}	mouse: 7 mg/m^3/2H		ND		ND
Intraperitoneal, LD_{50}	rat: 70 mg/kg mouse: 138 mg/kg guinea pig: 157 mg/kg	rat: 126 mg/kg mouse: 200 mg/kg	ND	rat: 165 mg/kg mouse: 100 mg/kg	ND
Intravenous, LD_{50}	mouse: 145 mg/kg rabbit: 100 mg/kg	mouse: 422 mg/kg	ND	cat: 175 mg/kg rabbit: 100 mg/kg	ND
Intravenous, LD_{lo}		rabbit: 100 mg/kg dog: 500 mg/kg monkey: 300 mg/kg	ND		ND

Source: NLM, 1995b

The ACGIH (1993) reviewed the available literature and reported that thioglycolic acid has toxicologic properties similar to those of acetic acid but is more penetrating and injurious than concentrated mineral acids of the same pH. Acute effects reported include the following.

Oral

- The oral LD_{50} of undiluted thioglycolic acid in rats is less than 50 mg/kg.
- In a single oral dose study conducted in female rats given 10% thioglycolic acid in water solution, death was first observed after intubation of 125 mg/kg. Necropsy indicated hepatic involvement; possible irritation of the gastrointestinal tract was accompanied by an increased degree of fluidity of the gastrointestinal contents.

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Inhalation

- Male rats that inhaled 620 ppm (at room temperature) or 8,200 ppm (heated to 125°C) thioglycolic acid for 7 hours showed no untoward effect during the exposure or during a 2-week postexposure observation period.

Topical

- The LD_{50} in rabbits through percutaneous absorption applying a 10% solution was 848 mg/kg (95% confidence limit, 505-1430 mg/kg).
- Fatalities were produced by topical application of a 10% solution to guinea pigs at less than 5 ml/kg. The signs of intoxication included weakness, gasping, and convulsions.
- Application of thioglycolic acid as a single dermal-application patch test in rabbits resulted in necrosis in 5 minutes. This was accompanied by local hyperemia and edema.

Eye

- Instillation of thioglycolic acid into the rabbit eye resulted in severe pain, severe conjunctival inflammation, dense corneal opacity, and severe iritis. These effects had not improved by 14 days after exposure; washing immediately after exposure did not modify the response.

In a safety assessment by the CTFA (1991), the reported animal toxicities of thioglycolic acid, ammonium thioglycolate, and sodium thioglycolic acid were summarized as follows.

Acute/Subchronic Toxicity

- No rats died after 1 hour of exposure to an aerosol containing 60.0% thioglycolic acid.
- Permanent wave solutions 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 monothioglycolate, concentrations up to 22.0%, and in a study in which rats were dosed with a 4% solution of glyceryl monothioglycolate. In a subchronic study, no significant gross lesions were observed in rats that were injected intraperitoneally with 100 mg/kg of 5.0% sodium thioglycolate.
- A permanent wave solution containing 10.98% ammonium thioglycolate and one containing 22% glyceryl monothioglycolate were practically nontoxic in rabbits in acute dermal toxicity studies. In a 21-day dermal toxicity study, 1 of 12 rabbits died after receiving 0.75 ml/kg doses of a 17.5% ammonium thioglycolate cold wave product for 2 days and 2.0 ml/kg doses of the diluted product for 3 days. 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 another dermal toxicity study, none of the rabbits died after an acid wave product containing 22.6% glyceryl monothioglycolate was applied 5 days per week for 4 weeks.

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- Transient conjunctival redness was observed in rabbits after the instillation of a cold wave product containing 17.5% ammonium thioglycolate. Minimal ocular irritation also was observed in rabbits after instillation of a commercial acid wave containing 22.0% glyceryl monothioglycolate.

- 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. Glyceryl monothioglycolate (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 monothioglycolate were applied.

- In open epicutaneous tests, repeated applications of 9% thioglycolic acid and 22% glyceryl monothioglycolate induced skin irritation, but not sensitization, in guinea pigs. In other epicutaneous tests, mild sensitization reactions were observed in guinea pigs challenged with 5% or 30% ammonium thioglycolate. There were no reactions to 0.2% or 1% ammonium thioglycolate. Results from open epicutaneous tests also indicated that glyceryl monothioglycolate 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 with ammonium thioglycolate concentrations that ranged from 0.5% to 7% did not induce sensitization.

- Minimal to slight hyperplasia of the thyroid occurred in diabetic and nondiabetic Osborne-Mendel rats administered sodium thioglycolate when weanling (21-day-old) rats were injected intraperitoneal 5 days per week with 100 mg/kg for 24 weeks and sacrificed at 6 months Freeman *et al*., 1956).

Chronic Toxicity

- There was no evidence of carcinogenicity in Swiss female mice or female rabbits that received dermal applications of 1.0% or 2% sodium thioglycolate in acetone twice per week throughout the study. Sodium thioglycolate was applied to the shaved skin (interscapular region) of each of 45 mice and to the inside of each of the left ear of 5 rabbits. Untreated and positive (7,12-dimethylbenz[α]anthracene treated) controls were included in the study. Mice were allowed to die spontaneously; rabbits were killed during the 85th week of treatment. Differences in the incidence of neoplasms between experimental and negative control mice were not significant; epidermal neoplasms were not observed. No neoplasms were observed in rabbits. No significant decrease in the life span of mice or rabbits in experimental groups compared to untreated controls was observed.

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Short-Term Tests:

Thioglycolic Acid. Thioglycolic acid (98% pure) tested negative at doses up to 3,333 µg/plate without metabolic activation and at doses up to 2,000 µg/plate with metabolic activation in a *Salmonella typhimurium* preincubation assay with strains TA100, TA1535, TA97, and TA98 (Zeiger *et al*., 1987).

In a safety assessment by the CTFA (1991), the reported mutagenicity of thioglycolic acid was summarized as follows.

- Thioglycolic acid was not mutagenic in the Ames assay using *Salmonella typhimurium* LT2 strains TA1535, TA1537, and TA1438. Thioglycolic acid (diluted with DMSO) was tested at concentrations of 1, 10, 100, and 1,000 µg/plate with and without metabolic activation.

- Thioglycolic acid was not mutagenic in strain Sd-4-73 of *Escherichia coli* via the paper disk method.

- A 0.5% solution of thioglycolic acid was not mutagenic in a sex-linked recessive lethal mutations test that used male flies (4-5 days old) of the Canton-S strain. The test solution was not mutagenic to any of the 309 X chromosomes tested.

Sodium Thioglycolate. In a safety assessment by the CTFA (1991), the reported mutagenicity of sodium thioglycolic was summarized as follows.

- Sodium thioglycolate was not mutagenic up to 3,600 µg/plate in a *Salmonella*/mammalian-microsome mutagenicity testing strains TA1535, TA100, TA1538, TA98, and TA1537 of *S. typhimurium*, without metabolic activation.

- In another study, the mutagenic potential of sodium thioglycolate (25mm in 5% saccharise) was evaluated using the sex-linked recessive lethal mutations test in Berlin K (wild type) and Basc strains of *Drosophila melanogaster*. Approximately 1200 X chromosomes were tested per experiment in each of three successive broods. F_2 progeny cultures with two or fewer wild-type males were routinely retested in the F_3 generation to confirm X-linked recessive lethal mutations. The test substance was not mutagenic.

- The mutagenic potential of sodium thioglycolate also was evaluated using the micronucleus test. Two hundred eighty five mg/kg of test substance was administered intraperitoneally 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 and one thousand polychromatic erythrocytes were scored. The test substance was not mutagenic.

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Sodium thioglycolate tested negative at doses up to 1,000 µg/plate with and without metabolic activation in a *Salmonella typhimurium* preincubation assay with strains TA100, TA1535, TA1537, and TA98 (Zeiger *et al*., 1987).

Ammonium Thioglycolate. In a safety assessment by the CTFA (1991), the reported mutagenicity of ammonium thioglycolic was summarized as follows.

- Ammonium thioglycolate was not mutagenic in the Ames assay using *Salmonella typhimurium* strains TA1535, TA1537, and TA1538. The concentrations tested ranged from 0.25 to 5.0 mg/plate in strain TA1535 and TA1538 cultures and from 0.5 to 5.0 mg/plate in strain TA1537 cultures.

Glyceryl Monothioglycolate. A safety assessment by the CTFA (1991) summarized the reported mutagenicity of glyceryl monothioglycolate as follows.

- Glyceryl monothioglycolate was not mutagenic in an Ames assay using strains TA1535, TA1537, and TA1538 of *S. typhimurium*. The concentrations tested ranged from 0.25 to 5.0 mg/plate.
- Glyceryl monothioglycolate was not mutagenic in an Ames assay using strains TA1538, TA98, TA100, and TA1537 of *S. typhimurium*. The concentrations tested ranged from 0.02 to 1.50 mg/plate with and without metabolic activation.

Metabolism: Current thinking on transdermal penetration of thioglycolic acid and glyceryl monothioglycolate would identify glyceryl monothioglycolate as the more significant skin penetrant. Upon skin penetration, the mercaptide of thioglycolic acid ($^{-}SCH_2COOH$) is neutralized to the mercaptan . The mercaptide of glyceryl monothioglycolate ($^{-}SCH_2COOG$) can exist in body fluids at physiological pH (CTFA, 1991).

In a safety assessment by the CTFA (1991), the reported absorption, distribution, metabolism, and excretion of thioglycolic acid, ammonium thioglycolate, and sodium thioglycolic acid were summarized as follows.

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

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

- Most of the radioactivity was excreted in the urine in the form of neutral sulfate 24 hours after 100 mg/kg of ^{35}S-thioglycolic acid was administered to groups of rats via intravenous and intraperitoneal injection. Similar results were noted after rabbits received 100 and 200 mg/kg doses of ^{35}S-thioglycolic acid. Significant concentrations of dithioglycolate were detected in the urine of rabbits 24 hours after thioglycolic acid (100-150 mg/kg) was injected intraperitoneally. Negligible concentrations of thioglycolic acid were detected. After a 5.0% solution of sodium thioglycolate (70, 80, and 123 mg/kg doses) was injected intravenously into rabbits, the tests 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 disulfide was not noted up to 10 hours after intraperitoneal injection of a rat with 150 mg/kg of sodium thioglycolate.

Other Biological Effects: In a safety assessment by the CTFA (1991), the biological effects of thioglycolic acid were summarized as follows.

- 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
- inhibition of fatty acid oxidation

Structure/Activity Relationships: Seven compounds structurally similar to thioglycolic acid were screened for relevant information associating these related chemicals with a mutagenic or carcinogenic effect. A summary of information found in the available literature is presented in Table 2 followed by a more detailed discussion. No information on carcinogenicity or mutagenicity was found for the following structurally related compounds: glycolic acid [79-14-1], thiodiglycolic acid [123-93-3], 2-mercapto propionic acid [79-42-5], 3-mercapto propionic acid [107-96-0], methyl thioglycolate [2365-48-2], and

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ethyl thioglycolate [623-51-8]. Information on mutagenicity was identified for the structurally related compound, 2-mercaptoethanol.

2-Mercaptoethanol. 2-Mercaptoethanol tested negative at doses up to 15 µmol/plate without metabolic activation in a *S. typhimurium* preincubation assay with strain TA100 (Carter & Josephry, 1986). Positive mutagenicity test results were reported in RTECS as follows.

- DNA damage in microorganisms at 10 mM (Lown & Sim, 1977)
- Inhibition of DNA synthesis in rat liver mitochondria at 1 mmol/L (D'Agostino *et al*., 1975)
- micronuclei cell induction in C3H mouse embryo cells at 100 mg/L (DeBrabander *et al*., 1976).

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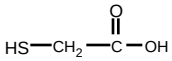
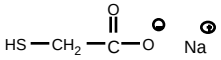
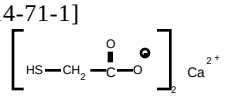
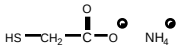
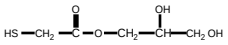
Table 2. Summary of Information on Thioglycolic Acid, Salts and Structurally Related Compounds

Chemical Name	Carcinogenicity Data	Mutagenicity Data
Thioglycolic Acid [68-11-1] 	NDF	negative in *S. typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, and TA1438 with and without activation (CTFA, 1991; Zeiger *et al*., 1987) negative in *E. coli* strain Sd-4-73 (CTFA, 1991) negative for sex-linked recessive lethal mutations in Canton-S flies (CTFA, 1991)
Sodium Thioglycolate [367-51-1] 	noncarcinogenic in mice or rabbits following lifetime dermal application of up to 2% (CTFA, 1991)	negative in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 with and without metabolic activation (CTFA, 1991; Zeiger *et al*., 1987) negative for sex-linked recessive lethal mutations in *Drosophila melanogaster* (CTFA, 1991) negative in the mouse micronucleus test (CTFA, 1991)
Calcium Thioglycolate [814-71-1] 	NDF	NDF
Ammonium Thioglycolate [5421-46-5] 	NDF	negative in *S. typhimurium* strains TA1535, TA1537, and TA1538 (CTFA, 1991)
Glyceryl Monothioglycolate [30618-84-9] 	NDF	negative in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 with and without metabolic activation (CTFA, 1991)
2-Mercaptoethanol [60-24-2] **$HS\text{-}CH_2\text{-}CH_2OH$**	NDF	negative in *S. typhimurium* strain TA100 without metabolic activation (Carter & Josephry, 1986) DNA damage in microorganisms (Lown & Sim, 1977) inhibition of rat liver mitochondrial DNA synthesis (D'Agostino *et al*., 1975) micronuclei cell induction in mouse embryo cells (DeBrabander *et al*., 1976)

NDF: no data found

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