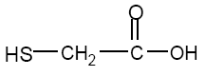
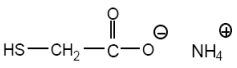
SIDS INITIAL ASSESSMENT PROFILE

Category name	Thioglycolic acid and its ammonium salt	
CAS No.	68-11-1	5421-46-5
Chemical Name	Thioglycolic acid	Ammonium thioglycolate
Structural Formula		

SUMMARY CONCLUSIONS OF THE SIAR

Analogue/Category rationale

The category comprises the 2 sponsored substances, thioglycolic acid and ammonium thioglycolate. One analogue of similar structure, sodium thioglycolate (CAS. 367-51-1) is used to fill data gaps where data are not available for the sponsored substances. These chemicals are grouped into a category based on similar molecular structure ($HS\text{-}CH_2\text{-}COO^-$, R^+ , where R = H^+, NH_4^+ or Na^+), functionality and (eco)toxicological properties. Both the carboxyl and the mercapto moieties of thioglycolic acid are acidic, in aqueous media, thioglycolic acid and its salts undergo full dissociation into the thioglycolate anion ($HS\text{-}CH_2\text{-}COO^-$) and the respective cations (H^+, NH_4^+ or Na^+). The toxicity of each compound is mainly driven by the thioglycolate anion. Sodium sulfate and ammonium chloride, sulfate and phosphate have previously been assessed in the OECD HPV Program[1] and according to the available data, the effect of the counter-ion (sodium or ammonium) on the systemic toxicity and the ecotoxicity of the thioglycolic salts is not expected to be significant.

Physical-chemical properties

Thioglycolic acid is a colorless liquid (with a characteristic sulfide odor) with a $pKa_{1(\text{-COOH})}$ ranging from 3.55 to 3.82 and $pKa_{2(\text{-SH})}$ from 9.30 to 10.23, a melting point of -16.2°C, a boiling point of 207.85 to 209.85°C at 1024 hPa (accompanied by decomposition) and a measured vapour pressure of 0.16 hPa at 25°C. The measured octanol-water partition coefficient (log K_{ow}) is 0.27 at pH 1.7 and 22°C and thioglycolic acid is highly soluble in water (>1000 g/L at 20°C).

The 71% aqueous solution of ammonium thioglycolate is a colorless to faint pink liquid (with a characteristic sulfide odor) with a melting point <-20°C, a boiling point of 115°C at 1021 hPa (decomposition between 165 and 267°C) and an estimated vapour pressure of 11.5×10^{-4} Pa at 25°C for the pure ammonium thioglycolate. The calculated log K_{ow} (from the measured value for thioglycolic acid at pH 1.7) is -2.99 at pH 7 and 22°C and ammonium thioglycolate is freely soluble in water at least up to a concentration of 71%.

Human Health

No data is available on the absorption of thioglycolic acid and/or its salts by inhalation or oral exposure. However, the physico-chemical properties of the thioglycolates, small ionisable water-soluble molecules with a very low logK_{ow} as well as the acute oral and inhalation toxicity data suggest that thioglycolic acid and/or its salts are significantly absorbed by the inhalation and oral routes. Regarding dermal absorption, no reliable data is available on the pure substances. However, studies performed with cosmetic formulations indicate a low dermal penetration (ca. 1%) for the ammonium salt.

[1] Ammonium chloride (CAS Reg. no. 12125-02-9) was submitted for review at SIAM 17 (JP/ICCA), ammonium sulfate (CAS Reg. no. 7783-20-2) at SIAM 19 (DE/ICCA), sodium sulfate (CAS Reg. no. 7757-82-6) at SIAM 20 (SK+CZ/ICCA) and diammonium phosphate (CAS No. 7783-28-0) at SIAM 24 (US/ICCA). The SIDS Dossiers are available on the OECD website: http://cs3-hq.oecd.org/scripts/hpv/

After i.v. injection, ^{35}S-thioglycolate is mainly distributed in the kidneys, lungs, and spleen of a female monkey, and in the small intestine and kidneys of a rat. Residual ^{35}S blood concentrations at 0.5 to 7 h post-injection did not exceed 5.3% in rats. Significant concentrations of dithiodiglycolate were detected in the urine of rabbits 24 h after thioglycolic acid was injected i.p. Negligible concentrations of thioglycolate were detected.

In a study performed according to the OECD Guideline 401, the oral administration of thioglycolic acid to male and female rats resulted to a LD_{50} of 73 mg/kg bw. Its ammonium (71% solution) and sodium salt administered orally to male and female rats gave LD_{50}'s between 50 and 200 mg/kg bw in OECD Guideline 423 studies. Behavioral abnormalities and in some cases, GI tract irritation, were the most common findings after oral administration. In a study performed according to the OECD Guideline 403, the exposure of male and female rats to a vapour/aerosol mixture of thioglycolic acid results in a LC_{50} of 2.172 mg/l for males and 1.098 mg/l for females. Clinical signs included a severe irritation of the respiratory tract and mucuous membranes and behavioural abnormalities, the lungs were discolourated at necropsy. A 7-hour inhalation exposure of male rats to saturated vapours generated at 125°C or ambient temperature produced no mortality or clinical signs of toxicity. In a non-guideline acute dermal toxicity study, the LD_{50} of thioglycolic acid was 848 mg/kg bw in male and female rabbits. The clinical signs were limited to skin irritation and necrosis at the sites of application. For the ammonium (71% solution) and sodium salts, the LD_{50}'s in male and female rats were >2000 mg/kg bw and between 1000 and 2000 mg/kg bw, respectively, in studies performed according to the OECD Guideline 402. No significant clinical signs of toxicity were reported.

Thioglycolic acid was corrosive to the skin in an EpiDerm Skin Model study performed according to Directive 2000/33/EC, B.27. It was also corrosive to the eyes in a study in rabbits compliant with the OECD Guideline 405. The ammonium and sodium salts are only slightly irritating for the skin and the eyes of rabbits in OECD Guideline 404 and 405 studies, respectively. Respiratory tract irritation was observed in rats exposed to a high concentration of a vapour/aerosol mixture, but not when exposed to saturated vapour only.

Due to its corrosive properties, the skin sensitisation potential of not neutralized thioglycolic acid has not been investigated. Thioglycolic acid salts are considered as skin sensitisers. The sensitising potential of ammonium and sodium salts of thioglycolic acid was investigated in a local lymph node assay in mice performed following the OECD Guideline 429. Both substances were found to be sensitising to the skin with an EC_3 value of 0.65% and ca. 6%, respectively. Due to a number of skin sensitisation in hairdressers caused by ammonium thioglycolate and due to positive test results in various dermal clinics the sensitizing effect of ammonium thioglycolate to the skin should be considered as certainty.

No reliable data is available on the repeated dose toxicity of thioglycolic acid and its ammonium salt. The repeated dose toxicity of sodium thioglycolate was evaluated by oral and dermal administrations.

In an oral repeated dose toxicity study compliant with the OECD Guideline 408, sodium thioglycolate was administered by gavage, 7 days per week, for 13 weeks, to male and female rats. Clear but fully reversible effects on some haematological and biochemical parameters and histopatholical changes in heart and liver were observed at 60 mg/kg bw/d. These effects may be related to the inhibition of the β-oxidation of fatty acids. The NOAEL was 20 mg/kgbw/d.

In a repeated dose dermal toxicity study completed by National Toxicology Program (NTP) and using a method comparable to the OECD Guideline 411, sodium thioglycolate was administered via dermal route, 5 days per week, for 13 weeks to male and female rats and mice. All animals survived the 13 weeks administration. The only treatment related effect was skin irritation at the site of application. The LOELs for skin irritation were 11.25 and 45 mg/kg bw/d and the NOAELs for systemic toxicity were higher than 180 and 360 mg/kg bw/d in rats and mice, respectively.

In reverse gene mutations assays with multiple strains of *Salmonella typhimurium* performed with methods compliant or comparable to the OECD Guideline 471, thioglycolic acid and its ammonium and sodium salts were not mutagenic in the presence and absence of metabolic activation. In a gene $TK^{+/-}$ mutation assay in mouse lymphoma L5178Y cells, performed following the OECD Guideline 476, ammonium thioglycolate was also not mutagenic in the presence and absence of metabolic activation. As well, thioglycolic acid was not clastogenic, with or without metabolic activation, in an *in vitro* chromosomal aberration assay in humam lymphocytes performed following the OECD Guideline 473. In a micronucleus assay on the peripheral blood of mice treated dermally for 13 weeks with sodium thioglycolate, a slight but statistically significant increase of the frequency of the micronucleated normochromatic erythrocytes was only observed in female mice at the top dose level of 360

mg/kg bw/day. This result seems of doubtful significance because thioglycolic acid did not induce structural chromosomal aberrations *in vitro*, and thioglycolic acid and its sodium salt failed to show any evidence of clastogenic potential when administered by the dermal and oral routes, up to the maximum tolerated dose, in two mouse bone marrow micronucleus assays performed following the OECD Guideline 474. In the sex-linked recessive lethal mutations test, sodium thioglycolate was not mutagenic. The weight of evidence suggests that thioglycolic acid and its salts are not genotoxic.

No data is available on the carcinogenic potential of the category members by the oral and inhalation routes. In a non-standard study by dermal route in mice, sodium thioglycolate was administered as 0, 1.0 and 2.0% solutions (0.02 ml per mice), respectively, until all animals died. Differences in the life span and the incidence of neoplasms between experimental and negative control mice were not statistically significant.

Thioglycolic acid and its salts are not considered to be reproductive toxicants, excepted at dose levels associated with maternal lethality. In a reproduction/developmental toxicity screening test performed following the OECD Guideline 421, sodium thioglycolate was administered by oral administration to rats, 10 weeks before mating and through mating and, for the females, through gestation until day 5 *post-partum*. The NOAEL for parental toxicity was considered to be 20 mg/kg bw/day (based on deaths at 40 and 80 mg/kg bw/day), the NOAEL for reproductive performance (mating, fertility and delivery) was considered to be 20 mg/kg bw/day (based on deaths at 40 and 80 mg/kg bw/day) and the NOAEL for toxic effects on progeny was 40 mg/kg bw/day (based on the dead litter at 80 mg/kg bw/day which cannot definitively be attributed to maternal condition).

In the 13-week dermal subchronic toxicity study in rats and mice with sodium thioglycolate, no treatment-related effects on sperm density and motility, caudal epididymal sperm, spermatid head counts in the testes and testis weights, as well as oestrous cycles, were observed up to dose levels of 180 and 360 mg/kg bw/day, respectively.

Thioglycolic acid and its salts are not considered to be developmental or toxicants, except at dose levels associated with maternal lethality. The developmental toxicity of sodium and ammonium thioglycolates has been investigated in standard oral and dermal studies in rats and/or rabbits compliant or comparable to OECD Guideline 414. Ammonium thioglycolate was administered by gavage to pregnant rats from gestational days 6-19. At 75 mg/kg bw/day, two animals died. The body weight, food and water consumption of the dams were not affected by the treatment. No embryo/fetal toxicity, or treatment-related teratogenicity was observed in any group. The NOAELs for maternal and embryo-foetal toxicity were 15 and 75 mg/kg bw/day, respectively. Sodium thioglycolate was topically applied to pregnant rats from gestational days 6-19 and to pregnant rabbits from gestational days 6-29. In rats, there was one reported maternal death at 200 mg/kg bw/day. Feed consumption, water consumption, and body weights of the dams all significantly increased. The body weights of the foetuses were significantly lower than the controls, however there was no other evidence of embryo/foetal toxicity. In rabbits, moderate to severe erythema occurred at the dosing site in all groups, however no maternal systemic toxicity, embryo/foetal toxicity, or treatment-related teratogenicity were observed in any group. The LOAELs for maternal toxicity was 50 mg/kg bw/day in rats and the NOAEL was 65 mg/kg bw/day (the highest dose tested) in rabbits. The developmental toxicity NOAEL was 100 mg/kg bw/day for rats and 65 mg/kg bw/day for rabbits.

No teratogenic effects were observed.

The mortality and the signs of systemic toxic observed in the oral acute or repeated dose toxicity studies seems primiraly linked to the inhibition of the β-oxidation of fatty acids. This inhibition induced secondary effects like a decrease of blood glucose, liver glycogen content, blood and hepatic ketone bodies and liver acetyl-CoA and an increase of plasma free fatty acids and liver triglycerides and acyl-CoA and an enhancement of hepatic pyruvate. The fatty liver induced by thioglycolate was mainly due to an inhibition of acyl-CoA dehydrogenase activity and consequently to a marked depression of the β-oxidation pathway.

Environment

With pKa_1 ranging from 3.55 to 3.82 and pKa_2 from 9.30 to 10.23 according to the sources, thioglycolate ion mainly exists in its dissociated form at environmentally relevant pH values. Thioglycolic acid and its salts are expected to oxidize in water abut are not expected to photolyse, due to lack of absorption in the environmental spectrum, and to volatilize. Based on thioglycolic acid and salts physico-chemical properties (high solubility and low Log P), it is considered that they are not expected to adsorb to suspended solids, sediments and soils and are mobile in soil.

Usually modeling approach is proposed to roughly estimate possible transport between environmental compartments. This approach cannot necessarily be followed for all categories of substances. Ionizable substances for instance do not fit in relevancy criteria of the common models used. Nevertheless, in some extent, physico-chemical information allows a certain understanding of the behaviour.

With a Henry's Law constant of 1.45 x 10^{-6} atm-m^3/mole, thioglycolic acid is expected to be essentially non-volatile from water and moist soil surfaces. Thioglycolic acid is not expected to volatilize from dry soil surfaces based upon an experimental vapor pressure of 16 Pa .

The main process which will lead to degradation of thioglycolic acid in water is a fast oxidation to dithiodiglycolate as demonstrated by literature and also practical cases. This result combined with available information related to biodegradation process of thioglycolate (OECD Guideline 301 B – 60% of biodegradation after 28 days) and dithiodiglycolate (OECD Guideline 301 B – 80% of biodegradation after 28 days) allows to conclude that thioglycolic acid and its salts are ready biodegradable.

Acute toxicity studies, carried out for thioglycolic acid according to OECD guidelines, reveal 96-hour LC_{50} of > 100 mg/L for fish (*Oncorhynchus mykiss*) and 48-hour EC_{50} of 38 mg/L for invertebrates (*Daphnia magna*) expressed as nominal concentrations as concentrations were maintained throughout the tests. Algae and daphnia tests carried out on thioglycolic acid oxidation product (diammonium dithiodiglycolate) demonstrate that the substance is not toxic to algae and daphnia with $EC_{50's}$ > 100 mg/L.

The only one data available for salts is related to fish acute toxicity of ammonium salt. The OECD Guideline 203 test reveals 96-hour LC_{50} > 100 mg/L (measured concentration) for *Oncorhynchus mykiss.*

Based on physico-chemical properties of the substances (high water solubility > 1000 g/L and low Log P = -2.99), the bioaccumulation potential is considered to be low.

Exposure

In 2008, the total world market was estimated to be close to 30,000 metric tons of thioglycolic acid equivalents. Thioglycolic acid is manufactured by the reaction of monochloracetic acid [79-11-8] or its salts with alkali hydrosulphides, eg, NaSH or NH_4SH, in aqueous medium. Ammonium thioglycolate is obtained by neutralisation of the acid with ammonia. Thioglycolic acid is used as a chemical intermediate for the synthesis of esters, which is in turn used as an intermediate for the synthesis of tin stabilizers for PVC. Salts of thioglycolic acid are used in cosmetics like permanents, hair straightening and depilatory preparations, in the leather industry and in some other industrial uses.

Monitoring data measured from effluents at production sites of the two major producers are below the detection limit. In the industry (manufacturer and processor), workers exposure to thioglycolic acid by inhalation and/or dermal contact would be expected to occur primarily during drumming operations. However, due to its corrosive nature, dermal exposure is avoided by the use of personal protective equipment. Limited data on the occupational exposure of professionals (21 hairdressing salons in Finland) to ammonium thioglycolate indicates a very low level of inhalation exposure, well below than the current occupational exposure limit of thioglycolic acid. However, a number of skin sensitisation cases in hairdressers caused by ammonium thioglycolate indicates a potential dermal exposure. Consumer exposure may occur by dermal contact through the use of personnal care products. Exposure via the environment is considered negligible.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health

Thioglycolic acid and its salts should be considered candidates for further work The chemicals in this category possess properties indicating a hazard for human health (acute toxicity, corrosivity (acid), sentitization and repeated dose toxicity studies). Thioglyoclic acid salts are present in consumer products. Member countries are invited to perform an exposure assessment, and if indicated a risk assessment.

Environment

Thioglycolic acid and its salts are of low priority for further work The chemicals in this category possess properties indicating a hazard for the environment (toxicity to aquatic invertebrates between 10 and 100 mg/L). However the chemicals are readily biodegradable and possess a limited potential for bioaccumulation.