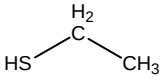
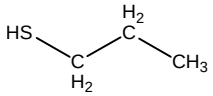
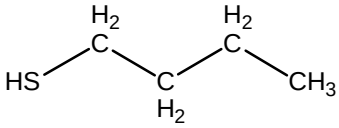
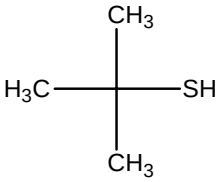
Category Name	C2-C4 Aliphatic Thiols Category
Chemical Names and CAS Nos.	**1-Ethanethiol (CAS No. 75-08-1)** **1-Propanethiol (CAS No.107-03-9)** **1-Butanethiol (CAS No.109-79-5)** **2-Propanethiol, 2-Methyl (CAS No. 75-66-1)**
Structural Formulae	 1-Ethanethiol (Ethyl Mercaptan)
	 1-Propanethiol (n-Propyl Mercaptan)
	 1-Butanethiol (n-Butyl Mercaptan)
	 2-Propanethiol, 2-Methyl (t-Butyl Mercaptan)

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The C2-C4 Aliphatic Thiols contain a sulfhydryl (SH) functional group with a straight or branched aliphatic carbon chain that characterizes the category. The four aliphatic thiols are soluble in water and have reasonably comparable melting points, initial boiling points and vapor pressures, as well as very low and objectionable odor thresholds. The water solubility and narrow range of octanol-water partition coefficients (log Kow) for the three linear C2-C4 Aliphatic Thiols indicate that they will have similar environmental fate and are not expected to bioaccumulate in aquatic organisms. Ecotoxicity is similar for the three linear C2-C4 Aliphatic Thiols with data for fish, invertebrate and algae toxicity indicating a similar order of acute toxicity across the chemicals tested (ecotoxicity is less for t-butyl-mercaptan). ECOSAR has been used to address and support the data gaps for the linear category members. Environmental fate and toxicity data are available for the branched t-butyl mercaptan. The available toxicology data show that the C2-C4 Aliphatic Thiols also have a similar order of toxicity under a variety of experimental conditions. In the WHO document (http://www.inchem.org/documents/jecfa/jecmono/v44jec09.htm), the applicability domain for the alkyl and aromatic thiols evaluated is much wider for simple, alkyl thiols and the "category" is based on the presumed common metabolism of these thiols. Simple thiols are metabolized via several different pathways in mammalian systems that include: S-methylation, resulting in a methyl thioether that would undergo S-oxidation; reaction with glutathione to form mixed disulfides (the likely form in circulation); and, especially for the low molecular weight thiols [methanethiol was presented as the example], oxidative desulfuration to yield CO and SO_4. From this information and available toxicity data, it can be concluded that the category members show a similar order of toxicity. Although the data for **n-butyl mercaptan** cannot be used for read-across purposes quantitatively, data can be used qualitatively to determine the hazard for these chemicals based on their common metabolic pathways. Therefore, although the specific test substance as described and discussed is referenced, the data satisfy the SIDS requirements for all four category members.

Physicochemical Properties

The C2-C4 mercaptans (ethyl, n-propyl, n-butyl, and t-butyl) are liquids at room temperature. The respective measured melting points are -147.8, -113.3, -115.9, and -0.5ºC; the measured boiling points are 35.1, 67.8, 98.5, and 64ºC; the measured vapor pressures are 705, 205, 60.6, 240 hPa (all at 25ºC); the measured water solubility values are 15600, 1900, 595, 1470 mg/L (at 25ºC, n-butyl at 20ºC) ; the octanol log K_{ow} values are 1.27 (predicted), 1.81 (measured), 2.28 (measured), 2.14 (predicted). The

pKa for all four mercaptans is 10.7.

Human Health

No toxicokinetic, metabolism or distribution studies were identified for any of the C2-C4 Aliphatic Thiols. A description of the likely metabolism of the C2-C4 Aliphatic Thiols is summarized above in Category Rationale.

In rats, 4-hour LC_{50} values for the C2-C4 Aliphatic Thiols via inhalation ranged from > 2.52 mg/L (for **ethyl mercaptan**) to 98.3 mg/L (for **t-butyl mercaptan**) in rats and mice. Clinical signs included lacrimation, hunched posture, tremors, staggering gait, muscular weakness, cyanosis, sedation. Irritation of the mucous membrane evidenced by rubbing of the eyes and nose, eye closure, watering of the eyes, corneal opacities and retracting of the head were also observed for **t-butyl mercaptan**. Respiratory tract irritation may occur following high exposures to the C2-C4 Aliphatic Thiols. The dermal LD_{50} values for all category chemicals ranged from 1682 mg/kg bw (for n-propyl mercaptan) to > 2000 mg/kg-bw for the other category mercaptans. Initial skin contact evoked a severe pain reaction with a slight darkening in the skin color. Erythema and thickened skin were the most common findings after dermal application of the C2-C4 Aliphatic Thiols. The oral LD_{50} for the C2-C4 Aliphatic Thiols in rats ranged from 682 mg/kg bw (for **ethyl mercaptan**) to 4729 mg/kg bw (for **t-butyl mercaptan**). In the oral studies, rats exhibited ruffled fur, docility, lacrimation, staggering, and blood stains around the nose and sedation at the higher doses.

Ethyl and n-propyl mercaptans were moderately irritating following 4-hour occluded exposure in rabbits; the irritation resolved within 24 hours. **n-Butyl and t-butyl mercaptans** were non-irritating in the same study design. In a second study, **n-propyl mercaptan** was minimally irritating to 3 of 6 rabbits following application for 4 hours under occlusive conditions (similar conditions to OECD TG 404). **n-Propyl mercaptan** was moderately irritating to the eyes of rabbits (similar conditions to OECD TG 405). All eyes were normal following a 7-day observation period. Based on the available data, the C2-C4 Aliphatic Thiols group chemicals are mild to moderate skin irritants to the rabbit skin and at most moderately irritating to rabbit eyes.

In the Buehler test under the EPA OPPTS 870.2600 test guideline, **t-butyl mercaptan** resulted in dermal scores (Grade 1-3) in guinea pigs at 24 and 48 hours following induction with a 100% solution and a challenge using a 75% solution. **t-Butyl mercaptan** was a skin sensitizer in guinea pigs. No skin sensitization data were available for ethyl, n-propyl, and n-butyl mercaptans. Based on the available data, the C2-C4 Aliphatic Thiols group chemicals are considered as skin sensitizers.

Repeated-dose toxicity has been investigated in 13-week inhalation toxicity studies with **n-butyl and t-butyl mercaptan** and an oral combined repeated-dose/reproductive/developmental toxicity study with **t-butyl mercaptan**. In the 13-week inhalation study (similar to OECD TG 413), rats (15/sex/concentration) were exposed (whole body) to **n-butyl mercaptan** vapor concentrations of 0, 9, 70, or 150 ppm (0, 0.033, 0.26 or 0.55 mg/L) for six hours per day, five days per week. Decreased red blood cells were observed for females at week 12 for the 70 ppm group and at weeks 6 and 12 for the 150 ppm group. A statistically significant elevation of neutrophils and a corresponding decrease of lymphocytes were noted for the 150 ppm group of females at week 12. None of these changes were out of the normal range for rats and therefore were not considered to be biologically significant. No effects on hematology parameters were observed in males. Lung weights were statistically significantly elevated for males at 70 and 150 ppm. The only histopathological finding attributable to the test material was the presence of increased macrophages of trace severity in the lungs of male and female rats in the 150 ppm group. The NOAEC and the LOAEC were 9 ppm (0.033 mg/L/day) and 70 ppm (0.26 mg/L/day), respectively. In the 13-week inhalation study (similar to OECD TG 413), rats (15/sex/concentration) were exposed to **t-butyl mercaptan** vapor concentrations of 0, 9, 97 or 196 ppm (0, 0.033, 0.36 or 0.72 mg/L) for six hours per day, five days per week. There were no deaths, clinical signs of toxicity or body weight changes observed. Differences in blood urea nitrogen and erythrocyte count observed at 6 and/or 12 weeks were within historical control ranges and were not considered toxicologically significant. No compound-related macroscopic lesions were observed in any of the rats that were sacrificed at the termination of the study or those that died during the course of the study. Toxicologically significant increases in the mean absolute and relative weight of the kidneys occurred in male rats exposed to 97 and 196 ppm. There was a compound- and concentration-related increase in chronic nephrosis (varying degrees of multifocal degeneration of the proximal convoluted tubules, tubular regeneration, and inflammatory cell infiltration of the interstitium) in 14 of 15 animals at the high concentration (196 ppm), 13 of 15 at the mid concentration (97 ppm) and 7 of 15 animals at the low concentration (9 ppm). Even though presence of α-2u-globulin was not assessed by appropriate staining in this study, it was done for the oral combined repeated-dose/reproductive/developmental toxicity screening test (42 – 53 days). Taking into account similar pathological findings on male rat kidney in both studies, it is assumed that effects found are indicative of α-2u-globulin nephropathy, which has no relevance to human health The NOAEC was established at 196 ppm (0.72 mg/L). Based on an increase of alveolar macrophages in male and female rats exposed to 97 and 196 ppm, the NOAEC for pulmonary irritation was established at 9 ppm (0.033 mg/L).

In the combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422), rats (12/sex/group in the main study and 5 males and 5 non-mated females in the recovery groups) were administered **t-butyl mercaptan** in corn oil by gavage at 0, 10, 50 or 200 mg/kg bw/day for 42-53 days. The recovery groups of control and high dose were monitored without

dosing for 2 weeks for recovery. Decreased body weight was observed in both sexes at 200 mg/kg bw/day throughout the administration period. During the recovery period, a lower body weight was observed in females, but body weight gains throughout the recovery period were similar to those of the control group. Decreased food consumption was observed in males at 200 mg/kg bw/day on days 4 and 15 of administration and in females at 200 mg/kg bw/day throughout the administration period. During the recovery period, females exhibited lower food consumption on day 1 of the recovery period, but food consumption after day 4 of the recovery period was similar to the control group. There was no effect on urinalysis measurements. For both sexes, changes in hematological and clinical chemistry parameters (either increases or decreases depending on the parameter) were observed at 50 and 200 mg/kg bw/day during dosing but only at 200 mg/kg bw/day during the recovery period. At necropsy, enlargement and discoloration of the kidneys were observed in 1, 3, and 4 males at 10, 50, and 200 mg/kg bw/day, respectively and liver enlargement was observed in 2 males at 200 mg/kg bw/day; after the recovery period, kidney enlargement was observed in 1 male at 200 mg/kg bw/day. No gross findings were recorded for females. Increases in absolute and relative liver weights were observed in males (50 and 200 mg/kg bw/day) and females (200 mg/kg bw/day). Kidney weight in males at 50 and 200 mg/kg bw/day and relative weight at all doses were significantly increased. A decrease in absolute thymus weight was observed in males at 200 mg/kg bw/day. Following the recovery period, increased relative liver weight was observed in both sexes and increases in absolute and relative weights of the kidneys were observed in males at 200 mg/kg bw/day. Histopathological changes were observed in the liver and spleen of both sexes and in the kidneys of males including: hepatocellular centrilobular hypertrophy in males at 50 and 200 mg/kg bw/day and in females at 200 mg/kg bw/day; hemosiderin deposits in the red pulp in the spleen of both sexes at 200 mg/kg bw/day; periportal fatty degeneration of hepatocytes in males at 50 and 200 mg/kg bw/day; basophilic renal tubules and hyaline deposits in proximal tubular epithelial cells in the kidneys in males at all doses which were considered to be indicative of α-2u-globulin nephropathy, which has no relevance to human health. Following the recovery period, hemosiderin deposits were observed in the red pulp of the spleen of both sexes, basophilic renal tubules were observed in the kidneys in males, and periportal fatty degeneration of hepatocytes was observed in 1 male and 1 female at 200 mg/kg bw/day. The NOAEL was 10 mg/kg/day for males and 50 mg/kg/day for females.

No reliable oral repeated-dose toxicity studies were identified for **ethyl, n-propyl**, or **n-butyl mercaptans**. Data for acute toxicity indicate that there are differences in potency between the shorter (C2) and longer chain (C4) aliphatic thiols. However, 13-week repeated-dose inhalation toxicity data show similar toxicity profiles for methyl mercaptan and butyl mercaptans (**n-butyl- and t-butyl-mercaptans**). The NOAEC value for these chemicals was 0.033 mg/L. Therefore, **n-** and **t-butyl mercaptans** data are used to read across to **ethyl-** and **n-propyl-mercaptans**. Methyl mercaptan was assessed at SIAM 27 and is not a member of this category.

Ethyl, n-butyl, and t-butyl mercaptans were not mutagenic in *in vitro* bacterial reverse mutation assays (OECD TG 471) with or without metabolic activation. In *in vitro* mammalian cell gene mutation (mouse lymphoma) assays (OECD TG 476), neither **n-butyl nor t-butyl mercaptan** induced mutagenic responses while **ethyl mercaptan**, at one intermediate dose (90.5 µg/ml), without activation, increased induction of mutations that was 2-fold greater than the negative control. Because only one dose level, in the absence of S9, elicited a 2-fold response, the results were considered to be equivocal. In an *in vitro* sister chromatid exchange assay (OECD TG 473), **n-butyl mercaptan** did not induce a statistically significant genotoxic effect. **Ethyl mercaptan** showed a positive response in this assay at the highest concentration; however, excessive cytotoxicity, as represented by limited numbers of cells to evaluate, may have caused the increase in sister chromatid exchanges (SCEs). No reliable *in vitro* genotoxicity studies were identified for n-propyl mercaptan. In an *in vivo* mouse micronucleus assay (OECD TG 474), **t-butyl mercaptan** did not induce chromosomal mutations. No *in vivo* genotoxicity studies were identified for **ethyl, n-butyl**, and **n-propyl mercaptan**. Overall, based on the weight of evidence, it is concluded that these compounds do not induce gene mutations in bacteria or chromosomal aberrations *in vivo* or *in vitro*.

No carcinogenicity studies were identified for any of the four compounds in the C2-C4 Aliphatic Thiols category.

t-Butyl mercaptan did not result in toxicity to the embryo or fetus or show developmental toxicity via gavage dosing to rats at doses as high as 200 mg/kg bw/day in the previously described combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422). Neonatal toxicity was evident at 200 mg/kg bw/day based on reduced body weights of the pups on PND4. For **n-butyl mercaptan**, the NOAEC for both maternal and fetal toxicity was 152 ppm (0.58 mg/L) in rats. In pregnant mice, mortality was observed at concentrations of 68 and 152 ppm (0.26 and 0.58 mg/L); however, no fetal toxicity was observed in surviving animals. The NOAEC for maternal toxicity was 10 ppm (0.038 mg/L) and 68 ppm (0.26 mg/l) for developmental toxicity. For **t-butyl mercaptan**, no exposure-related maternal or fetal toxicity occurred in rats or mice at exposures up to 195 ppm (0.72 mg/L). No reliable fertility/developmental toxicity studies were identified for ethyl or n-propyl mercaptans. Based on these screening-level results, the C2-C4 Aliphatic Thiols are not likely to result in reproductive or developmental toxicity.

Limited reports from human volunteer studies and reports of accidental exposure suggest that 3-hour exposure to 10 mg/m^3 (4 ppm) **ethyl mercaptan** gave rise to nausea, headaches, fatigue and irritation of mucous membranes of the lips, mouth and nose.

Exposure at 1 mg/m^3 (0.5 ppm) produced no unpleasant symptoms. Human volunteers exposed to ethyl mercaptan at 10 mg/m^3 (4 ppm) 3 hr daily during 5-10 days, showed minimal effects such as rise in olfactory threshold and altered taste reaction to bitter and sweet substances. Volunteers also reported periodic nausea, irritation of mucous membranes of lips, mouth, and nose and sensation of fatigue.

These chemicals possess properties indicating a hazard for human health (mild to moderate skin and eye irritation, potential skin sensitization, and repeated-dose toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The C2-C4 Aliphatic Thiols do not react with water; the only functionality other than carbon-hydrogen bonds is the sulfhydryl group. Predicted atmospheric oxidation half lives (AOP v. 1.92) for these chemicals are 3.2 hours (**ethyl mercaptan**), 3.0 hours (**n-propyl mercaptan**), 2.9 hours (**n-butyl mercaptan**), and 3.9 hours (**t-butyl mercaptan**). There are no photoreactive groups in these molecules and, therefore, direct photolysis is not expected.

The level III fugacity model (EpiSuite 4.00) calculation for **ethyl mercaptan** with equal and continuous release (1000 kg/hr) to air, water, and soil, is 6.9% to air, 75% to water, 17% to soil, and 0.2% to sediment; for **n-propyl mercaptan** it is 6.0% to air, 68% to water, 25% to soil, and 0.2% to sediment; for **n-butyl mercaptan** it is 5.7% to air, 58% to water, 36% to soil, and 0.2% to sediment; and for **t-butyl mercaptan** it is 9.0% to air, 71% to water, 20% to soil, and 0.3% to sediment.

Three of the four C2-C4 Aliphatic Thiols have been evaluated in biodegradation studies conducted according to OECD TG 301D. **n-Propyl and n-butyl mercaptans** are readily biodegradable based on the Guideline criteria with 84.7% and 91.8% degradation after 28 and 14 days, respectively, with both meeting the 10-day window. For **ethyl mercaptan**, biodegradation reached 27.1% after 28 days and, therefore, it was not readily biodegradable. Due to tertiary branching, it is expected that t-butyl mercaptan is not readily biodegradable. A study evaluating the biodegradability of t-butyl mercaptan is in progress. Calculated Henry's law constants (HENRYWIN v. 3.0) for these chemicals are, for **ethyl mercaptan**: 3.5 x 10^2 Pa-m^3/mole (3.5 x 10^{-3} atm-m^3/mole), for **n-propyl mercaptan**: 4.7 x 10^2 Pa-m^3/mole (4.6 x 10^{-3} atm-m^3/mole), for **n-butyl mercaptan**: 6.2 x 10^2 Pa-m^3/mole (6.1 x 10^{-3} atm-m^3/mole), and for **t-butyl mercaptan**: 6.2 x 10^2 Pa-m^3/mole (6.1 x 10^{-3} atm-m^3/mole). These values suggest that volatilization of these chemicals from the water phase is expected to be high. Based on the estimated log Kow values of these chemicals (1.27 – 2.28) and water solubility (595 – 15,600 mg/L), their bioaccumulation potential is expected (BCFBAF v. 3.00) to be low (estimated BCF = 3.2, 7.3, 15 and 12 for **ethyl**, **n-propyl**, **n-butyl** and **t-butyl mercaptans**, respectively).

The following aquatic acute toxicity results have been determined for the members of this category:

Endpoint **CAS No.**	**Ethyl Mercaptan** **75-08-1**	**n-Propyl Mercaptan** **107-03-9**	**n-Butyl Mercaptan** **109-79-5**	**t-Butyl Mercaptan** **75-66-1**
Fish 96-h LC_{50} (mg/L)	**2.4 (m)** [a] 4.8 (e)	**1.3 (m)**[a] 2.9 (e)	No data 1.7 (e)	**34 (m)**[a] 2.0 (e)
Aquatic Invertebrates 48-h EC_{50} (mg/L)	**< 0.1 (LOQ) (m)** [b] **0.38 (m; 24 h)**[b] 0.65 (e)	**0.07 (m)**[b] 0.50 (e)	No data 0.38 (e)	**6.7 (m)**[b] 0.42 (e)
Algae 72-h EC_{50} (mg/L) 72-h NOEC (mg/L) 96 h EC_{50}	**0.76 (m; biomass)** **3.0 (m; growth rate)**[c] **0.1 (m:biomass)** **0.83 (m; growth rate)** [c] 0.35 (e)	No data 0.29 (e)	No data 0.22 (e)	**12(m; biomass)** [c] **24 (m; growth rate)** [c] **<6.41(m; biomass)** [c] **6.41(m; growth rate)** [c] 0.25 (e)

m= measured; e = ECOSAR predicted value; a: *Oncorhynchus mykiss* - (OECD TG 203); b: *Daphnia magna* - (OECD TG 202);

c: *Pseudokirchneriella subcapitata* - (OECD TG 201)

These chemicals possess properties indicating a hazard for the environment (acute toxicity to fish, invertebrates and algae from <1 to 100 mg/L). n-Propyl and n-butyl mercaptans are readily biodegradable. Ethyl mercaptan is not readily biodegradable and t-butyl mercaptan is expected to be not readily biodegradable. However, bioaccumulation potential for these chemicals is expected to be low. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Programme.

Exposure

As reported to the U.S. Environmental Protection Agency (U.S. EPA) for the year 2005, companies produced or imported between 450-4500 metric tons (1 million to < 10 million pounds) each of n-propyl and n-butyl mercaptan, and between 4500-22,500 metric tons (10 million to < 50 million pounds) each of ethyl and t-butyl mercaptan.

All of the C2-C4 Aliphatic Thiols are produced by the reaction of hydrogen sulfide with ethylene, isobutylene, propylene, or butane-1, to produce **ethyl**, **n-propyl**, **n-butyl**, or **t-butyl mercaptan**, respectively, followed by purification by distillation.

Thiols possess a sulfhydryl group (-SH) that is instrumental in introducing a sulfur group into various biologically active molecules in the pharmaceutical and agrochemical industries. Thiols are used as closely-controlled intermediates in the production of pesticides; for example, thiols are used in the production of thiocarbamates for herbicides and thiophosphates for insecticides. Thiols also have antioxidant properties that render them useful as polymer additives. The odor detection characteristics of the lower molecular weight thiols and the low order of mammalian toxicity makes them ideally suited for use as odorants in commercial applications, including addition to propane and natural gas as detailed for ethyl mercaptan and t-butyl mercaptan below. Odor thresholds for **ethyl**, **n-propyl**, **n-butyl** and **t-butyl mercaptans** are estimated to be 0.1 – 1.0 ppb, 1.6 ppb, 0.1 – 1.0 ppb and 0.08 ppb, respectively.

Thiols comprise the family of organic sulfur compounds. In general, these compounds exist naturally (water, plants, soil) and are required for survival of all higher organisms. **Ethyl mercaptan** is generated from vegetables (e.g. cabbage), natural gas wells, coal tar and mammalian excretory products. **n-Propyl mercaptan** is released from freshly crushed onions and related plant bulbs and **butyl mercaptans** are components of skunk secretions. Some bacterial systems have been shown to utilize thiols as their direct source of sulfur, specifically degrading the materials by selective cleavage of the C-S linkage. Other microorganisms are capable of releasing lower thiols from larger sulfur compounds.

When they are used in closely-controlled reactions as intermediates in agrochemical and other industrial production, exposure to the C2-C4 Aliphatic Thiols is expected to be low. Residual mercaptans in finished products, except where used for odorants, are not expected because of the high reactivity and the need to remove the thiols due to odor. When used as odorants, due to very low odor thresholds (as noted above), even low concentrations of the C2-C4 Aliphatic Thiols can be detected. Thus, as an example, the low ppm level of ethyl mercaptan in propane is sufficient to alert people of a propane leak well before 20% of the lower explosive limit (LEL) of propane in air is reached (the LEL for propane is approximately 4-5%, so 1% propane in air is insufficient to present an explosive hazard and the ethyl mercaptan is present at <1ppm which is a sufficient concentration to allow a leak to be detected). For t-butyl mercaptan, it is added to natural gas by natural gas delivery companies in closely-controlled conditions. The target amount is approximately 0.5-1.0 lb odorant blend per 1 million standard cubic feet of gas.