Sodium and Potassium xanthate salts: Human health tier II assessment

10 March 2017

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Carbonodithioic acid, O-ethyl ester, potassium salt	140-89-6
Carbonodithioic acid, O-(1-methylethyl) ester, potassium salt	140-92-1
Carbonodithioic acid, O-(1-methylethyl) ester, sodium salt	140-93-2
Carbonodithioic acid, O-butyl ester, potassium salt	871-58-9
Carbonodithioic acid, O-(3-methylbutyl) ester, potassium salt	928-70-1
Carbonodithioic acid, O-pentyl ester, potassium salt	2720-73-2
Carbonodithioic acid, O-(2-methylbutyl) ester, potassium salt	2720-75-4
Carbonodithioic acid, O-hexyl ester, potassium salt	2720-76-5

Chemical Name in the Inventory	CAS Number
Carbonodithioic acid, O-(2-methylpropyl) ester, sodium salt	25306-75-6
Carbonodithioic acid, O-(2-methylpropyl) ester, potassium salt	13001-46-2
Carbonodithioic acid, O-(1-methylpropyl) ester, sodium salt	36551-21-0

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are O-alkyl dithiocarbonate (xanthate) salts that are generally used as flotation agents in the mining industry. These chemicals have been grouped together for assessment due to their similar toxicological properties and uses. The chemicals in this group assessment are referred to as the following:

- carbonodithioic acid, O-ethyl ester, potassium salt (CAS No. 140-89-6): potassium ethyl xanthate;
- carbonodithioic acid, O-(1-methylethyl) ester, potassium salt (CAS No. 140-92-1): potassium isopropyl xanthate;
- carbonodithioic acid, O-(1-methylethyl) ester, sodium salt (CAS No. 140-93-2): sodium isopropyl xanthate;
- carbonodithioic acid, O-butyl ester, potassium salt (CAS No. 871-58-9): potassium butyl xanthate;
- carbonodithioic acid, O-(3-methylbutyl) ester, potassium salt (CAS No. 928-70-1): potassium isoamyl xanthate;
- carbonodithioic acid, O-pentyl ester, potassium salt (CAS No. 2720-73-2): potassium amyl xanthate;
- carbonodithioic acid, O-(2-methylbutyl) ester, potassium salt (CAS No. 2720-75-4): potassium 2-methylbutyl dithiocarbonate;
- carbonodithioic acid, O-hexyl ester, potassium salt (CAS No. 2720-76-5): potassium hexylxanthate;
- carbonodithioic acid, O-(2-methylpropyl) ester, sodium salt (CAS No. 25306-75-6): sodium isobutyl xanthate;
- carbonodithioic acid, O-(2-methylpropyl) ester, potassium salt (CAS No. 13001-46-2): potassium isobutyl xanthate; and
- carbonodithioic acid, O-(1-methylpropyl) ester, sodium salt (CAS No. 36551-21-0): sodium sec-butyl xanthate.

Priority Existing Chemical (PEC) reports have been published for a structurally related chemical, sodium ethyl xanthate (CAS No. 140-90-9; NICNAS, 1995; NICNAS, 2000). The chemicals in this group are expected to exhibit similar toxicity to sodium ethyl xanthate. These chemicals are produced by the reaction of an alcohol with sodium or potassium hydroxide and carbon disulfide (CAS No. 75-15-0). The chemicals readily decompose to carbon disulfide in the presence of moisture and/or heat. Given that carbon disulfide is toxic and highly flammable, a major decomposition product and a metabolite of the chemicals in this group, the health hazards of carbon disulfide are considered in this group assessment, where relevant.

Import, Manufacture and Use

Australian

Both sodium isopropyl xanthate and sodium isobutyl xanthate are listed on the 2006 High Volume Industrial Chemicals List (HVICL) with total reported volumes of 1000–9999 tonnes each.

Sodium isopropyl xanthate and sodium isobutyl xanthate have reported commercial use as flotation agents in the mining and metal extraction industry.

No specific Australian use, import, or manufacturing information has been identified for other chemicals in this group.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers, Galleria Chemica, the Substances and Preparations in Nordic countries (SPIN)

database, the Organisation for Economic Co-operation and Development High Production Volume chemical program (OECD HPV), the United States (US) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR) and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

Potassium ethyl xanthate, sodium isopropyl xanthate, potassium butyl xanthate, potassium isoamyl xanthate, potassium amyl xanthate, sodium isobutyl xanthate and potassium isobutyl xanthate have reported commercial use as flotation agents.

Potassium ethyl xanthate, sodium isopropyl xanthate and potassium butyl xanthate have reported site-limited uses including as:

- intermediate in organic synthesis; and
- additive in plastics manufacture.

Potassium ethyl xanthate, potassium butyl xanthate, potassium amyl xanthate and potassium hexyl xanthate have reported site-limited uses including as:

- intermediates in organic synthesis; and
- additives in rubber production.

Potassium ethyl xanthate, potassium butyl xanthate and sodium isopropyl xanthate have reported non-industrial uses including as:

- herbicides; and
- defoliants.

No specific international use, importation, or manufacturing information has been identified for other chemicals in the group.

Restrictions

Australian

No known restrictions have been identified.

International

Salts of O-alkyldithiocarbonic acids are listed on the following:

- EU Cosmetic Regulation 76/ 768/EEC Annex II— List of substances which must not form part of the composition of cosmetic products.
- The Association of South East Asian Nations (ASEAN) Annex II—Part I: List of substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’).

Potassium isopropyl xanthate and sodium isopropyl xanthate are specifically identified.

Existing Worker Health and Safety Controls

Hazard Classification

Sodium isopropyl xanthate is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

Acute toxicity – category 4; H302 (Harmful if swallowed)

Skin irritation – category 2; H315 (Causes skin irritation)

Exposure Standards

Australian

No specific exposure standards are available.

International

Potassium isopropyl xanthate has an exposure limit of 1 mg/m^3 time weighted average (TWA) in Latvia and Russia.

Health Hazard Information

Where toxicological data are lacking for any one chemical in this group, data available for the other chemicals in this group are used to ‘read-across’ for the hazard assessment. In addition, the structurally related chemical, sodium ethyl xanthate (CAS No. 140-90-9; NICNAS, 1995; NICNAS, 2000; REACHd), or other xanthates are considered relevant for ‘read-across’ for hazard assessment. Given that carbon disulfide (CAS No. 75-15-0) is a metabolite and a decomposition product of the chemicals in this group, the health hazards of carbon disulfide (NICNASa) are also considered relevant and are applied to this assessment where appropriate.

Toxicokinetics

Xanthates are metabolised in humans and animals to carbon disulfide. In a metabolism study, humans and guinea pigs were dosed with various xanthates and the amount of expired carbon disulfide was monitored.

Guinea pigs were administered 70–200 mg/kg bw of potassium ethyl xanthate by subcutaneous injection. Up to 7 % of the injected dose was expired as carbon disulfide after eight hours, with maximum elimination between 1–2 hours in most animals. Elimination of sodium ethyl xanthate when administered by subcutaneous injection at doses of 50 or 100 mg/kg bw was more rapid, with maximum elimination of carbon disulfide at one hour and complete elimination after six hours. In human volunteers orally administered sodium ethyl xanthate at doses of 150 or 250 mg/kg bw, maximum elimination of carbon disulfide in breath was between 1–2 hours following administration with complete elimination by six hours. This study also found that alcohol increases the rate and extent of carbon disulfide elimination in breath (NICNAS, 2000).

Carbon disulfide is metabolised in the liver by the cytochrome P-450 monooxygenase system to an unstable intermediate which spontaneously generates atomic sulfur, carbonyl sulfide or carbon dioxide. Alternatively, hydrolysis occurs to form atomic sulfur and monothiocarbonate, which are then eliminated as carbonyl sulfide and carbon dioxide in breath, and inorganic sulfates and organosulfur compounds in the urine (NICNASa).

Acute Toxicity

Oral

Sodium isopropyl xanthate is classified as hazardous with hazard category ‘Acute Toxicity Category 4’ and hazard statement ‘Harmful if swallowed’ (H302) in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). The available data indicate that the chemicals in this group have low to moderate acute oral toxicity in rats and mice, supporting the extension of this classification to the chemicals in this group (see **Recommedation** section).

The oral median lethal dose (LD50) values for potassium isopropyl xanthate in rats and mice are 1700 and 583 mg/kg bw, respectively. Reported signs of toxicity included excitement and muscle contraction (NICNAS, 1995; RTECS).

The oral LD50 values for sodium isopropyl xanthate, potassium amyl xanthate and sodium isobutyl xanthate in rats are 1250, 1000–2000 and 500 mg/kg bw, respectively. Reported signs of toxicity included increased motor activity, cyanosis, irritability, increased respiration and convulsions with death occurring 1–2 hours after administration of the chemicals. The chemicals produced adverse effects on the central nervous system (CNS), liver and kidneys (NICNAS, 1995; REACHa; REACHb; REACHc).

Dermal

No data are available for the chemicals in this group. Read-across data from a structurally similar chemical, sodium ethyl xanthate, indicate that the chemical has moderate acute toxicity in animal tests following dermal exposure, warranting hazard classification. Based on the similar toxicological profiles, the data available support the extension of this classification to the chemicals in this group (see **Recommedation** section).

The dermal LD50 for sodium ethyl xanthate in rabbits is <1000 mg/kg bw. Reported signs of toxicity included oedema and pigmentation of the skin with death occurring within 24 hours. It is noted that sulfide odour was present during the study, suggesting that the chemical has decomposed (NICNAS, 1995; REACHa; REACHb).

Inhalation

No data are available for the chemicals in this group or their analogues. Carbon disulfide has moderate acute toxicity in animal tests following inhalation exposure, warranting hazard classification (NICNASa; REACHa; REACHb). If carbon disulfide is present due to external decomposition from the chemicals in this group, the appropriate exposure controls should be applied.

Observation in humans

Several case reports were available on the accidental exposure of workers to the structurally related chemical, sodium ethyl xanthate, or to carbon disulfide resulting from the breakdown of sodium ethyl xanthate.

In one report, a worker who opened a tank containing sodium ethyl xanthate lost consciousness. On revival, it was reported that he was restless, vomited, had convulsive twitching of muscles in his arms and legs, difficulty in breathing, teary eyes and hoarseness. The worker later developed photophobia and fluid accumulation in the eyelids and eye discharge (REACHa; REACHb).

In another case report, a worker was dermally exposed to xanthate powder and solution (specific chemical was not specified) during a mixing process. Extensive skin contamination of the chest area of the worker was evident with green staining. The worker was reported with gastrointestinal symptoms which began 20 hours after exposure and lasted for three days. Carbon disulfide body burden was confirmed by the detection of 2-thiothiazolidine-4-carboxylic acid in the urine (<4 mg/L measured approximately 68 hours after exposure). However, it was unknown if the symptoms observed were caused by inhalation of carbon disulfide as a decomposition product or dermal exposure to xanthate/carbon disulfide (NICNAS, 2000; REACHa; REACHb; REACHc; REACHd).

Corrosion / Irritation

Skin Irritation

Sodium isopropyl xanthate is classified as hazardous with hazard category 'Skin irritation – category 2' and hazard statement 'Causes skin irritation' (H315) in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). The available data indicate that the chemicals in this group are irritating to the skin, supporting the extension of this classification to all chemicals in this group (see **Recommedation** section).

In an acute dermal irritation/corrosion study conducted according to OECD Test Guideline (TG) 404, 0.5 mL of sodium isobutyl xanthate in water (equivalent to 228 mg) was applied occlusively to the shaved skin of three male New Zealand White rabbits for four hours. Erythema (score of 4) and oedema (score of 3) were observed in all animals and persisted up to 72 hours in two animals. Bloody effusions and moderate swelling were observed one hour following application, and tinea was observed on the application sites at 24, 48 and 72 hours after application. The chemical was concluded to be highly irritating to rabbit skins (REACHc).

In an acute dermal irritation/corrosion study conducted according to OECD TG 404, 0.5 mL of the structurally related chemical, sodium ethyl xanthate in water (equivalent to 228 mg), was applied occlusively to the shaved skin of three male New Zealand White rabbits for four hours. Erythema (score of 4) and oedema (maximum score of 3) were observed in all animals and persisted up to 72 hours in two animals. Bloody effusions and moderate swelling were observed one hour following application, and tinea was observed on the application sites at 24, 48 and 72 hours after application. The chemical was concluded to be highly irritating to rabbit skins (REACHd).

The structurally related chemical, sodium ethyl xanthate, was applied occlusively to the shaved abdomen of rabbits at 1 mL/kg (10 % aqueous solution) or at 1000 mg/kg (pure chemical mixed with water to form a paste). The chemical as a 10 % solution did not cause skin irritation in rabbits. Irritant effects including oedema and pigmentation of the skin were observed in the animals treated with 1000 mg/kg of the chemical. The chemical was concluded to be a skin irritant (NICNAS, 1995; REACHa; REACHb).

Eye Irritation

The available data indicate that the chemicals in this group are severely irritating to the eyes, warranting hazard classification (see **Recommedation** section).

In an acute eye irritation and corrosion study conducted according to OECD TG 405, 0.1 mL of sodium isobutyl xanthate in water (equivalent to 45.61 mg) was instilled into the conjunctival sac of the right eye of a male rabbit. Cloudy corneal surface, congested iris, redness of the conjunctivae, oedema and discharge on the eyelid were observed one hour after instillation. The pupil was visible in the lower part of the eye and reacted slowly to light, and details of the iris were not visible at 24 and 48 hours after instillation. The effects worsened on the seventh day of observation with necrosis observed in the conjunctiva of the lower eyelid. The chemical was concluded to be corrosive to rabbit eyes in this study (REACHc).

In an acute eye irritation/corrosion study conducted according to OECD TG 405, 0.1 mL of the structurally related chemical, sodium ethyl xanthate in water, was instilled into the conjunctival sac of the right eye of a male New Zealand White rabbit. Congested iris, redness of the conjunctivae, oedema and discharge on the eyelid were observed one and 24 hours following instillation of the chemical. Half of the corneal surface was clouded, the pupil was visible in the lower part of the eye and reacted slowly to light, and details of the iris were not visible at 48 hours after instillation. These effects became more intense on the seventh day of observation (REACHd).

A 0.05 mL aliquot of the structurally related chemical, sodium ethyl xanthate (10 % aqueous solution), was instilled into the conjunctival sac of the left eye of each albino rabbit (three animals). Mild irritation was observed immediately following instillation of the chemical. One animal showed slight irritation at four hours after instillation but the effects were reversed on the following day. No other irritant effects were observed in this study (NICNAS, 1995; REACHa; REACHb).

Approximately 30 mg of the structurally related chemical, sodium ethyl xanthate (powder form), was applied to the conjunctival sac of the left eye of each albino rabbit (three animals). Marked irritation, scrambling, excitement and evidence of pain were observed immediately following application. Lacrimation and phonation were observed in one animal each. Moderate irritation and oedema of the eyelids were observed one hour after application. These effects were reversible within three days in two animals and five days in the remaining animal. It is noted that the effects could be due to physical irritation caused by the powder in the eyes. The chemical was concluded to be a moderate irritant in this study (NICNAS, 1995; REACHa; REACHb).

Sensitisation

Respiratory Sensitisation

Limited data are available. Potassium amyl xanthate was reported to not be a respiratory sensitiser. Based on the similar toxicological profiles, the data available support this conclusion for the chemicals in this group.

In a repeated inhalation toxicity study, Sprague Dawley (SD) rats (10 males/group), Swiss Webster mice (10 males/group), New Zealand White rabbits (four males/group) and beagle dogs (two males/group) were exposed to potassium amyl xanthate as aqueous aerosol at concentrations of 0, 23 or 252 mg/m^3 for six hours/day, five days/week for one month. No signs of respiratory sensitisation were observed in the animals (REACHa; REACHb).

Skin Sensitisation

Sodium isopropyl xanthate was reported to be a skin sensitiser in guinea pigs and potassium isoamyl xanthate was a skin sensitiser in a local lymph node assay (LLNA), warranting hazard classification. Based on the similar toxicological profiles, the data available support the extension of this classification to the chemicals in this group (see **Recommedation** section).

In a guinea pig maximisation test on sodium isopropyl xanthate, the guinea pigs (ten animals/sex) were induced by intradermal injections (two 0.1 mL of Freund's complete adjuvant, two 0.1 mL of the chemical in solvent, and two 1:1 mixture of the chemical and adjuvant) on the shoulders. One week after the injection, 10 % of the chemical in water was applied occlusively for 48 hours to the same area. Two weeks later the animals were challenged by an occlusive dermal application with 5 % of the chemical for 24 hours. Erythema was observed following the topical challenge and the chemical was concluded to be a skin sensitiser in guinea pigs (US EPA, 1999).

In a local lymph node assay (LLNA) conducted according to OECD TG 409, potassium isoamyl xanthate was applied topically to the dorsal surface of the ears of female CBA mice (five animals/group) at concentrations of 2.5, 5, 10, 25 or 50 % for three consecutive days. The mean stimulation indices were 1.57, 2.21, 2.94, 4.12 and 4.59 for the 2.5, 5, 10, 25 and 50 % dilutions, respectively. The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 10.77 %, indicating sensitisation potential (REACHd; REACHe).

Repeated Dose Toxicity

Oral

Potassium butyl xanthate has harmful repeated dose toxicity based on results from animal tests following oral exposure. However, it is noted that the study had limited reporting. In the absence of more comprehensive information, there is insufficient evidence to recommend hazard classification for the chemicals in this group.

In a subchronic oral toxicity test, potassium butyl xanthate was orally administered at a concentration of 10 mg/kg to rats, rabbits and dogs for four months. From weeks 6–7 of the study, clinical effects including rapid breathing, cyanosis, hair loss and dermatitis were observed. Loss of weight and increases in blood sugar and cholesterol were observed later. From week nine of the study, convulsions and paralysis of the extremities were observed in some animals. Mortalities were observed in some animals during the study period. No further details were provided. The lowest observed adverse effect level (LOAEL) was 10 mg/kg in this study (NICNAS, 1995; REACHa; REACHb; REACHc; REACHd).

Dermal

No data are available for the chemicals in this group.

Inhalation

Potassium amyl xanthate was reported to have harmful repeated dose toxicity based on results from animal tests following inhalational exposure, warranting hazard classification. Based on the similar toxicological profiles, the data available support the extension of this classification to the chemicals in this group (see **Recommedation** section).

In a repeated dose inhalation toxicity study, Swiss Webster mice (10 males/group), SD rats (10 males/group), New Zealand White rabbits (four males/group) and Beagle dogs (two males/group) were exposed to potassium amyl xanthate as aqueous aerosol at concentrations of 0, 23 or 252 mg/m^3 for six hours/day, five days/week for one month. Mortalities were observed in all original as well as 5/6 replacement mice in the 252 mg/m^3 group. Amongst these mice, five showed convulsions and hyperactivity prior to death. Higher liver to body weight ratio was observed in the mice of both treatment groups. Higher liver to body weight ratio, an increase in the absolute kidney weight (in males only), high serum alanine aminotransferase activity and microscopically visible granular degeneration of the renal tubular epithelial cells were observed in the rats of the 252 mg/m^3 group. Marked elevations of liver enzyme activities and hepatocellular degeneration, necrosis and inflammation were observed in the dogs of both treatment groups. No effects were observed in the treated rabbits. The chemical was concluded to have adverse effects on the CNS and liver in mice, the liver and kidneys in rats and the liver in dogs when exposed repeatedly through inhalation (NICNAS, 1995; REACHa; REACHb; REACHc).

Genotoxicity

Potassium isoamyl xanthate is not considered to have genotoxic or mutagenic potential based on several in vitro genotoxicity assays. Sodium ethyl xanthate, is not classified as genotoxic (NICNAS, 1995; NICNAS, 2000).In vivo genotoxicity data on carbon disulfide, a metabolite of the chemicals in this group, indicate that the chemical has limited genotoxic potential. The available data do not warrant hazard classification for the chemicals in this group.

In vitro studies

A bacterial point mutation assay was conducted according to OECD TG 471 in five *Salmonella typhimurium* strains (TA 97, TA98, TA100, TA102 and TA1535) up to a maximum concentration of 5000 µg/plate of potassium isoamyl xanthate, in the absence or presence of a rat liver metabolic activation system. Negative results were obtained in this study (REACHe).

A chromosomal aberration test was conducted according to OECD TG 473 in human lymphocytes. Potassium isoamyl xanthate, was tested up to maximum concentrations of 666 and 1000 µg/mL in the absence or presence of a rat liver metabolic activation system, respectively. The chemical did not induce significant increases in the number of cells with chromosome aberrations in the absence or presence of the metabolic activation. The chemical was concluded to not have clastogenic potential in this study (REACHe).

A mammalian cell gene mutation assay was conducted according to OECD TG 476 in the mouse lymphoma L5178Y TK+ cell line. Potassium isoamyl xanthate, was tested up to a maximum concentration of 900 µg/mL in the absence or presence of a rat liver metabolic activation system. The chemical induced significant increases in the mutation frequency in the absence of the metabolic activation (REACHe).

In vivo studies

No in vivo studies are available for assessment of the chemicals in this group or their analogues. In vivo data for the metabolite, carbon disulfide, were assessed for the genotoxic potential of the chemicals in this group.

In a micronucleus test conducted according to OECD TG 474, CD-1 mice (10 animals/sex/group) were exposed by snout-only inhalation to carbon disulfide at concentrations of 0, 467, 1558, 4675 mg/m^3 for six hours. Bone marrow cells were collected 24 and 48 hours after administration of the chemical and the polychromatic erythrocytes (PCEs) for each mouse were examined. No increases in micronucleated PCEs were found; thus, the chemical was concluded to be non-mutagenic in this study (REACHa; REACHb).

No significant increases in the frequency of chromosomal aberrations in bone marrow cells, dominant lethal mutations or sperm abnormalities were observed in rats exposed to carbon disulfide at concentrations of 63 or 125 mg/m^3, seven hours/day for one or five days. It is noted that the lack of sperm abnormalities was also observed in the positive control animals, indicating a problem with the test methods in the study (NICNASa; REACHa; REACHb).

In a separate study, oral exposure of carbon disulfide to pregnant rats on gestational days (GDs) 10–13 induced chromosomal aberrations and polyploid cells in the bone marrow of the animals as well as the embryos. According to the reviewer, the validity of these findings was difficult to assess as the statistical significance and the effective dose were not reported, except that it was 1/10 of the LD50 (NICNASa; REACHa; REACHb).

Carcinogenicity

No data are available for the chemicals in this group.

Reproductive and Developmental Toxicity

No data are available for the chemicals in this group or their analogues. Carbon disulfide is classified as hazardous—Category 3 substance toxic to reproduction—with the risk phrases 'Possible risk of impaired fertility' (Xn; R62) and 'Possible risk of harm to the unborn child' (Xn; R63). Given that carbon disulfide is a metabolite of the chemicals, the data available support the extension of this classification to the chemicals in this group (see **Recommedation** section).

In a reproductive toxicity study, male Long-Evans rats (24 animals/group) were exposed to carbon disulfide as vapour at concentrations of 0 or 1870 mg/m^3, six hours/day, five days/week for 10 consecutive weeks. The treated animals had significant reduction in weight gain and effects on mating behaviours, including decreased mount and ejaculation latencies, and decreased sperm counts in the ejaculate. The authors suggested that the chemical did not exert a direct effect on the testes. Instead, the chemical might interfere with processes regulating the transportation and ejaculation of the sperm (REACHa; REACHb).

In a one-generation study, female SD rats (15 animals/treatment group; 24 animals/control group) were exposed to carbon disulfide as vapour at concentrations of 0, 389, 777 or 1554 mg/m^3, six hours/day for 14 days before mating. The animals were then paired with untreated males and exposure to the chemical continued throughout mating and until GD 19. Exposure at 1554 mg/m^3 resulted in maternal and developmental toxicity, including decreased gestational body weight and food consumption, obstructed labour and increased pup mortality. No toxicity to fertility was observed in any animal. A no observed adverse effect concentration (NOAEC) of 777 mg/m^3 for maternal and developmental toxicity was established in this study, while the NOAEC for toxicity to fertility was 1554 mg/m^3 (REACHa; REACHb).

In a prenatal developmental toxicity study conducted according to OECD TG 414, pregnant New Zealand White rabbits (24 animals/group) were exposed to carbon disulfide as vapour at concentrations of 0, 190, 316, 948, 1896 or 3792 mg/m^3 for six hours/day on GDs 6–18. Maternal toxicity including ataxia, reduction in food consumption, laboured respiration, wheezing, tremors, abortion and mortality in two animals were observed at 3792 mg/m^3. Significantly higher incidences of post-implantation loss and total resorption, as well as significantly reduced mean foetal body weight were observed at 1896 and 3792 mg/m^3. Significant increases in skeletal and visceral malformation were observed at 3792 mg/m^3, although no single malformation accounted for this increase. In the other treatment groups, significant increases in skeletal malformation were observed, including incidences of rudimentary 13th ribs, extra ribs, extrathoracic vertebrae and hypoplastic pubis. These effects were reported to not be dose-related (NICNASa; REACHa; REACHb).

In a prenatal developmental toxicity study, pregnant CD rats were administered carbon disulfide by oral gavage at concentrations of 0, 100, 200, 400 or 600 mg/kg bw/day on GDs 6–15. The animals were euthanised on GD 20. Rough or erect coat, lethargy, postural abnormalities and hind limb paralysis were observed in the treated animals. Significant decreases in absolute maternal body weight gain and increases in relative liver weights, along with decreases in foetal body weights, were observed in the 200, 400 and 600 mg/kg bw/day groups. No treatment-related increases in malformation were observed in the offspring (REACHa; REACHb).

In a separate prenatal developmental toxicity study, artificially inseminated New Zealand White rabbits were administered carbon disulfide by oral gavage at concentrations of 0, 25, 75 or 150 mg/kg bw/day on GDs 6–19. All animals were euthanised on GD 30. Dose-related increases in maternal (decreased body weight gain, increased liver weights and mortality) and foetal (increased resorption) toxicity were observed in the treated animals. A significant increase in malformed foetuses was observed at 150 mg/kg bw/day, indicating developmental toxicity at doses not leading to marked maternal toxicity (REACHa; REACHb).

Male Charles-Foster rats (10 animals/group) were administered carbon disulfide at concentrations of 0, 25, 50, 100 or 200 mg/kg bw/day for 30 consecutive days via intraperitoneal (i.p.) injection. Significant decreases in serum testosterone levels and marked degenerative changes in the testicular tissue were observed in all treatment groups. The observations indicate that exposure to the chemical via i.p. injection induces adverse effects on the male reproduction system (REACHa; REACHb).

Observation in humans

Several epidemiological studies have indicated adverse reproductive effects after exposure to carbon disulfide. Menstrual disorders or spontaneous abortion were observed in several studies of female viscose/rayon workers exposed to the chemical at levels of below 3 ppm for three years or around 10 ppm for an unspecified period. Decreased serum oestradiol and progesterone and increased serum testosterone, prolactin and serotonin were also observed in female synthetic fibre workers when exposed to the chemical at levels around 3–7 ppm. Decreased libido and changes in sperm cell morphology were observed in male workers exposed to the chemical at levels around 13–26 ppm but with excursions up to 250 ppm (NICNAS, 1995; NICNAS, 2000).

Other Health Effects

Neurotoxicity

Oral exposure to xanthates produced adverse effects on the CNS in animal studies. In chronically exposed workers, behavioural and neurophysiological changes, reduced nerve conduction velocity, peripheral neuropathy and polyneuropathy were observed (see **Acute toxicity** and **Repeated dose toxicity** sections). In addition, repeated exposure to carbon disulfide were reported to induce neurotoxic effects. When exposed to carbon disulfide by inhalation, animals were present with reduced brain weight, ataxia and axonal swelling (NICNAS, 1995; NICNAS, 2000; NICNASa).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (neurotoxicity, reproductive and developmental toxicity), systemic acute effects (acute toxicity from oral and dermal exposure) and local effects (skin sensitisation). The chemicals can also cause harmful effects following repeated exposure through inhalational exposure, and skin and eye irritation. Decomposition of the chemicals to carbon disulfide may also lead to acute inhalation effects.

Public Risk Characterisation

Given there are no consumer uses identified for the chemicals in this group, it is unlikely that the public will be exposed. Hence, the public risk from these chemicals is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalational exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term, acute and local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalational exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of these chemicals is considered to be sufficient, provided that the recommended amendment to the hazard classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemicals are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

Sodium isopropyl xanthate is already classified as hazardous in HCIS for acute toxicity - Category 4 (H302) and skin irritation - Category 2 (H315) (Safe Work Australia).

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302) Toxic in contact with skin - Cat. 3 (H311)
Irritation / Corrosivity	Not Applicable	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Not Applicable	May cause damage to organs through prolonged or repeated exposure through inhalation - Cat. 2 (H373)
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging fertility or the unborn child - Cat. 2 (H361fd)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalational exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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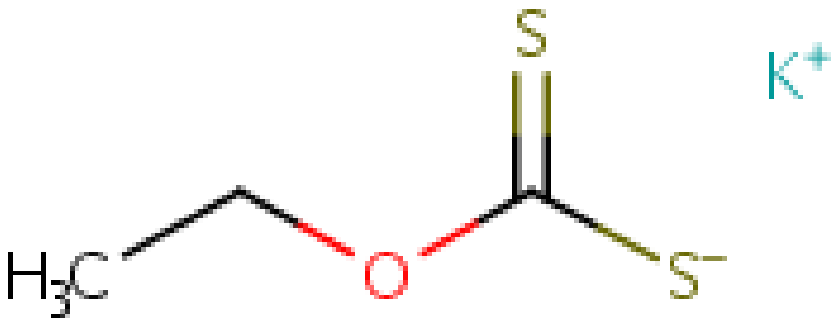
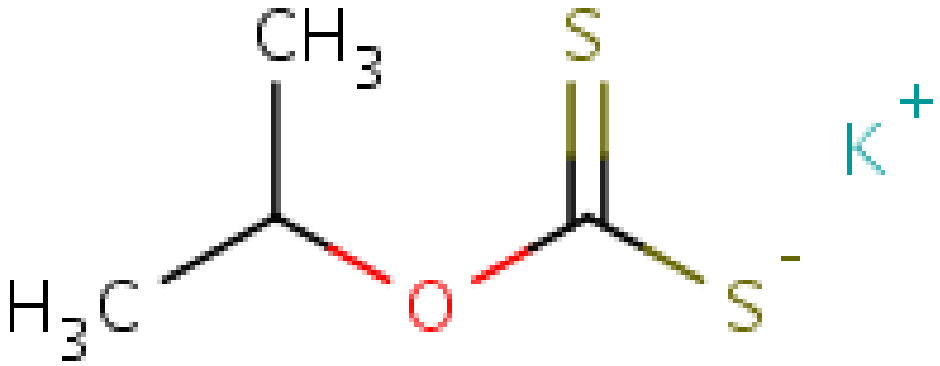
Last Update 10 March 2017

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Carbonodithioic acid, O-ethyl ester, potassium salt** potassium ethylxanthate ethyl potassium xanthate

CAS Number	140-89-6
Structural Formula	
Molecular Formula	C3H6OS2.K
Molecular Weight	160.3

Chemical Name in the Inventory and Synonyms	**Carbonodithioic acid, O-(1-methylethyl) ester, potassium salt** potassium isopropylxanthate dithiocarbonic acid O-isopropyl ester potassium salt potassium O-isopropyldithiocarbonate proxan potassium
CAS Number	140-92-1
Structural Formula	

	
Molecular Formula	C4H8OS2.K
Molecular Weight	174.328

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	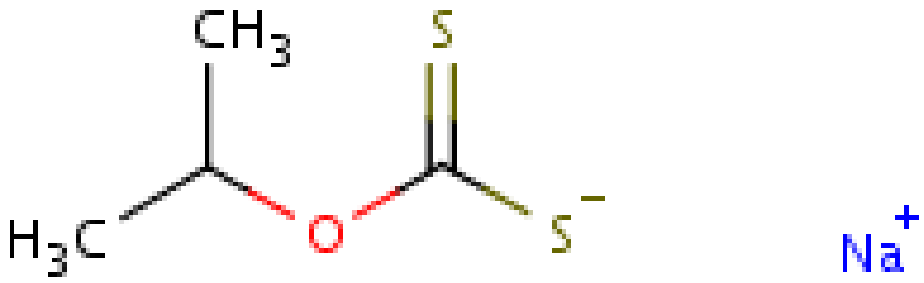
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	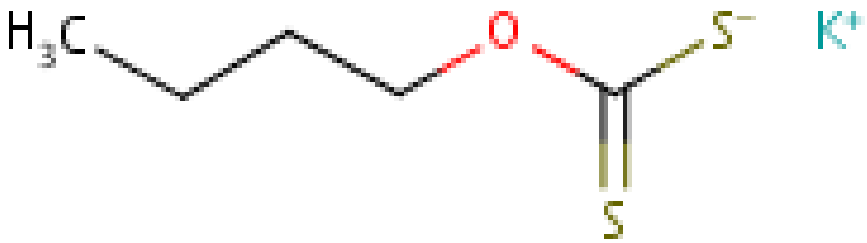
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Molecular Weight	188.3

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	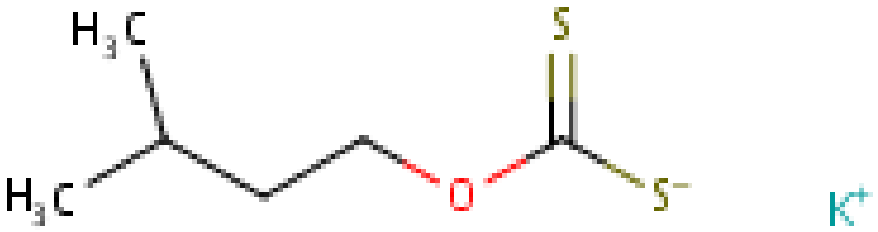
Molecular Formula	C6H12OS2.K
Molecular Weight	202.3

Chemical Name in the Inventory and Synonyms	**Carbonodithioic acid, O-pentyl ester, potassium salt** potassium amyl xanthate dithiocarbonic acid O-pentyl ester potassium salt potassium pentyl xanthate xanthic acid, pentyl-, potassium salt
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	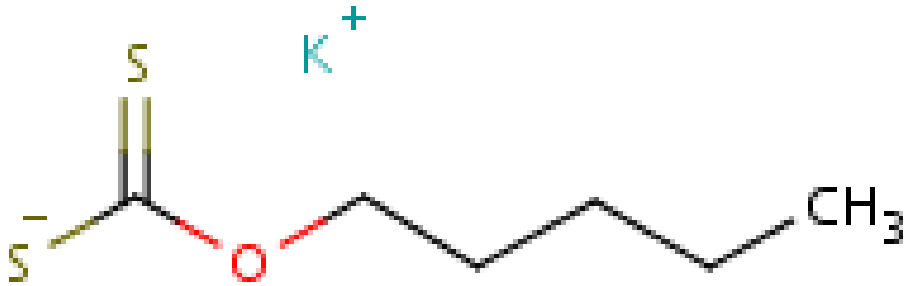
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Chemical Name in the Inventory and Synonyms	**Carbonodithioic acid, O-(2-methylbutyl) ester, potassium salt** potassium 2-methylbutyl dithiocarbonate O-(2-methylbutyl)carbonodithioate, potassium salt
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	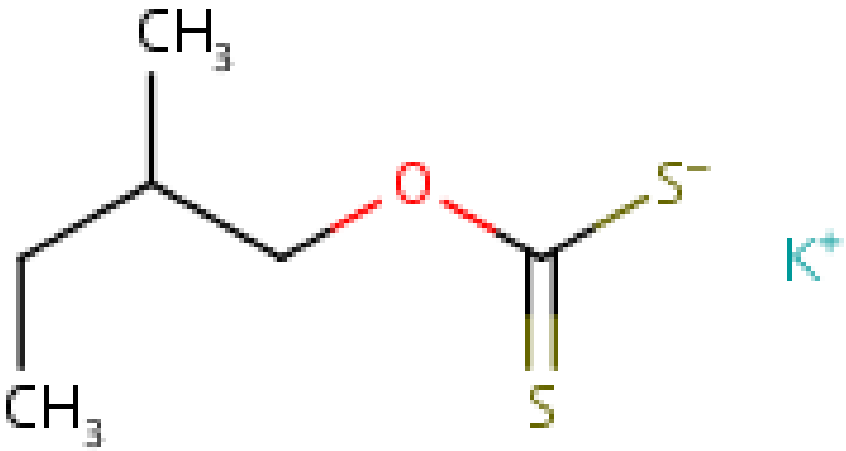
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Molecular Weight	202.3

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	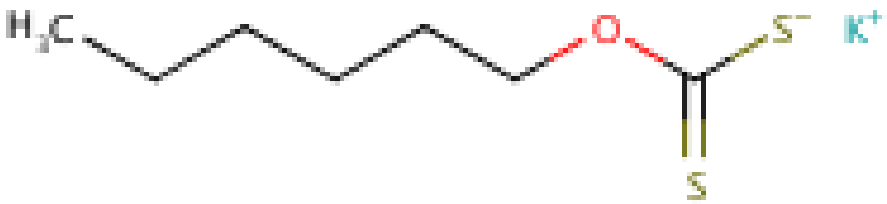
Molecular Formula	C7H14OS2.K
Molecular Weight	216.4

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	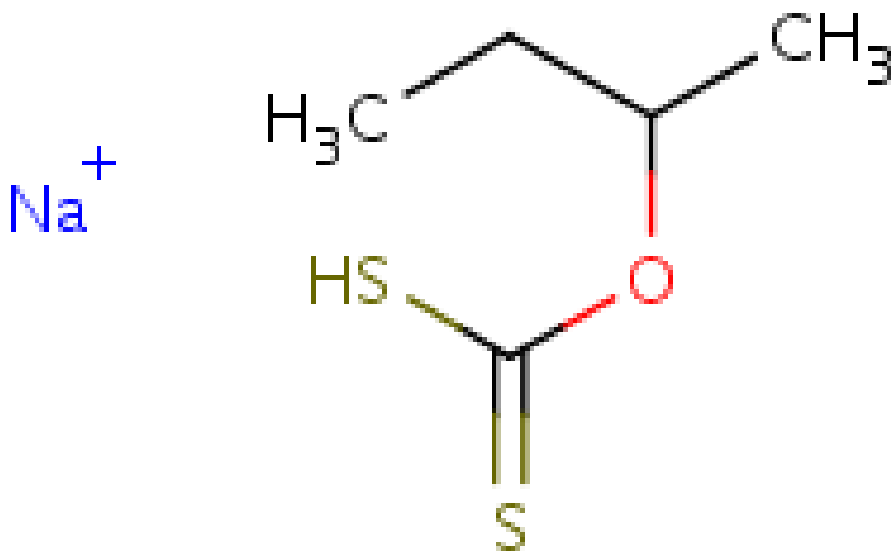
Molecular Formula	C5H10OS2.Na
Molecular Weight	173.255

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	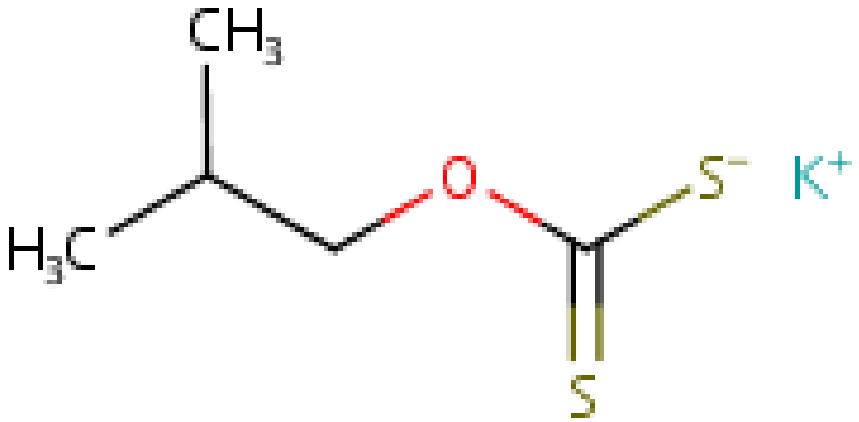
Molecular Formula	C5H10OS2.K
Molecular Weight	188.3

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	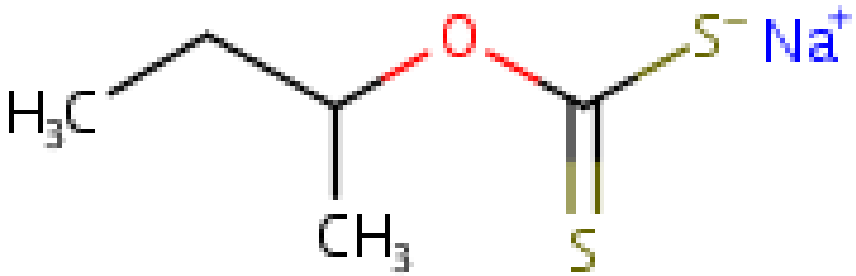
Molecular Formula	C5H10OS2.Na
Molecular Weight	172.2

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