2-(1-methylethoxy)ethanol and its acetate: Human health tier II assessment

28 June 2013

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Ethanol, 2-(1-methylethoxy)-	109-59-1
Ethanol, 2-(1-methylethoxy)-, acetate	19234-20-9

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

Limited data are available for 2-(1-methylethoxy)ethyl acetate (CAS No. 19234-20-9). The acetate is expected to rapidly metabolise to 2-(1-methylethoxy)ethanol (CAS No. 109-59-1). Data for other ethylene glycols and their acetates support the similarity of the toxicological profile of the acetate ester and the parent glycol ether. Uses of the chemical overseas do not significantly differ.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacture information has been identified.

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; and eChemPortal; OECD High Production Volume chemical program—OECD HPV; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource—ACToR and the US National Library of Medicine's Hazardous Substances Data Bank—HSDB.

No domestic uses for 2-(1-methylethoxy)ethyl acetate have been identified. The chemical 2-(1-methylethoxy)ethanol has reported domestic use including:

- in paints, lacquers and varnishes; and

- as a cleaning and washing agent.

This domestic use was reported in the SPIN database. Total use of this chemical in Nordic countries in 2011 was less than 5 tonnes. There is no consumer use of this chemical in Japan (OECD, 2009). The absence of the chemical from the available product ingredient databases indicates that it is not likely to be widely available for domestic use.

The chemicals have reported commercial use including:

- as a solvent for industrial painting processes;
- in publishing and printing; and
- as a reprographic agent.

The chemicals have reported site-limited use including:

- in rubber and plastic product manufacturing.

Restrictions

Australian

The chemicals fall within the scope of ethylene glycol monoalkyl ethers and their acetates, which are listed in Schedule 6 of the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) for preparations containing more than 10 % glycol ether (SUSMP, 2012). Schedule 6 chemicals are labelled with 'POISON'. These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label.

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

The chemical 2-(1-methylethoxy)ethanol is classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xn; R20/21 (acute toxicity)

Xi; R36 (irritation)

The chemical 2-(1-methylethoxy)ethyl acetate is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

The chemical 2-(1-methylethoxy)ethanol has an exposure standard of 25 mg/m^3 (106 ppm) time weighted average (TWA). No specific exposure standards are available for the acetate.

International

The following exposure standards are identified (Galleria Chemica) for 2-(1-methylethoxy)ethanol:

- an exposure limit (OEL, TWA, STEL, PEL or STV) of 5–25 mg/m3 (22–106 ppm) in different countries such as USA, Canada, Denmark, Germany, Norway and Switzerland.

No specific exposure standards are available for the acetate.

Health Hazard Information

Given the rapid metabolism of 2-(1-methylethoxy)ethyl acetate (CAS No. 19234-20-9) to 2-(1-methylethoxy)ethanol (CAS No. 109-59-1), data for 2-(1-methylethoxy)ethanol is considered representative of the toxicity of both chemicals in this group. Data for other ethyleneglycol ethers (of similar molecular weight) and their acetates has also been provided as supporting data. This includes 2-propoxyethanol (EGPE) (CAS No.2807-30-9), 2-butoxyethanol (CAS No. 111-76-2) and 2-butoxyethanol acetate (EGBEA) (CAS No. 112-07-2).

Toxicokinetics

2-(1-methylethoxy)ethyl acetate is expected to rapidly metabolise to 2-(1-methylethoxy)ethanol.

In general, ethylene glycol alkyl ethers are substrates for alcohol dehydrogenase isoenzyme ADH-3, which catalyses the conversion of the terminal alcohol to an aldehyde (which is a transient metabolite). Further rapid conversion of the aldehyde by dehydrogenase produces the alkoxyacetic acid, which is excreted in the urine.

In an intraperitoneal study with 2-(1-methylethoxy)ethanol in rats and dogs, the majority of the dose (88 %) was excreted within 24 hours. The main urinary metabolites in both species were isopropoxyacetic acid and N-isopropoxyacetylglycine. Ethylene glycol was also observed in the urine of rats. (OECD, 2009; REACH).

Acute Toxicity

Oral

The chemicals are expected to be of low acute toxicity based on animal test data for 2-(1-methylethoxy)ethanol. The median lethal dose (LD50) in rats following oral exposure is >2000 mg/kg bw. Observed sub-lethal effects included reduced body weight, reddish urine and a decrease in faecal volume (OECD, 2009; REACH).

Dermal

The chemical 2-(1-methylethoxy)ethanol is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in HSIS (Safe Work Australia). The available data (LD50 (male rabbits)—1440 mg/kg bw) support this classification (REACH). Details of signs of toxicity were not provided.

As the chemical 2-(1-methylethoxy)ethanol is considered representative of the toxicity of the acetate, 2-(1-methylethoxy)ethyl acetate is considered to be of moderate acute toxicity following dermal exposure.

Inhalation

The chemical 2-(1-methylethoxy)ethanol is classified as hazardous with the risk phrase ‘Harmful by inhalation’ (Xn; R20) in HSIS (Safe Work Australia). The available data (which indicate a median lethal concentration—LC50—between 2 and 20 mg/L (vapour)) support this classification (REACH). Reported signs of toxicity include hematuria and damage to the kidneys.

Significant increase in osmatic fragility of ethrocytes was observed in female rats exposed to 62 ppm of 2-(1-methylethoxy)ethanol. No effect was noted at 32 ppm. (ACGIG, 2011).

As 2-(1-methylethoxy)ethanol is considered representative of the toxicity of the acetate, 2-(1-methylethoxy)ethyl acetate is considered to be of moderate acute toxicity following inhalation exposure.

Corrosion / Irritation

Respiratory Irritation

No signs of respiratory irritation were observed in acute and repeat dose inhalation studies with 2-(1-methylethoxy)ethanol.

Skin Irritation

Based on the available data the chemicals are expected to cause slight to moderate irritation to the skin.

Skin irritation for 2-(1-methylethoxy)ethanol was determined in rabbits following the Draize method. 2-(1-methylethoxy)ethanol was classified a moderate irritant (Primary Irritation index 4.8) (OECD, 2009; REACH). Individual animal scores were not available. The relative scores at the abraded and non-abraded sights could not be determined from the available data. Therefore sufficient data was not available to allow comparison with classification criteria.

EGPE and EGBEA (analogue chemicals) are reported to be slightly irritating to skin in animal studies, particularly following repeated exposure. Effects were not sufficient to warrant a hazard classification (NICNASa; NICNASb).

Eye Irritation

The chemical 2-(1-methylethoxy)ethanol is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The available data generally support this classification, although the data were not directly comparable to classification criteria.

In an eye irritation study in rabbits, the chemical was found to be irritating with marked conjunctival irritation, marked corneal injury, and some iritis observed. Effects were reversible within seven days (REACH). The analogue EGPE is also classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS with available data supporting the classification (NICNASa).

Based on data for EGBEA (NICNASb), 2-(1-methylethoxy)ethyl acetate may only be slightly irritating to the eye.

Sensitisation

Skin Sensitisation

In general, monoalkyl glycol ethers and their acetates do not appear to be sensitisers. The negative results seen for, 2-(1-methylethoxy)ethanol in a guinea pig maximisation test (REACH), and the analogues EGPE and EGBEA (NICNASa; NICNASb), support a conclusion that the chemicals are not skin sensitisers.

Repeated Dose Toxicity

Oral

In a 28-day oral gavage study in rats (OECD TG 407), with 2-(1-methylethoxy)ethanol, a lowest observed adverse effect level (LOAEL) of 30 mg/kg bw/day was reported based on effects in bone marrow. Effects observed at higher concentrations (125 mg/kg bw/day and 500 mg/kg bw/day) included:

- haemolytic effects; increased liver, kidney and spleen weights; and
- histopathological changes in spleen and bone marrow.

Effects in the bone marrow and histopathological changes appeared reversible, although some changes in haematological parameters (increased MCV—mean corpuscular volume and MCH—mean corpuscular hemoglobin; decreased MCHC—mean corpuscular hemoglobin concentration) were observed at the end of the recovery period.

Similar effects were observed in a reproductive and developmental screening test with 2-(1-methylethoxy)ethanol in rats (41–48 day exposure). The no observed effect level (NOAEL) for this study was 30 mg/kg bw/day in males and 8 mg/kg bw/day in females. The NOAEL in females was based on reddish urine observed in one female dosed with 30 mg/kg bw/day.

Dermal

No data are available.

Inhalation

In a 28-day repeated dose inhalation (whole-body exposure) toxicity study (OECD TG 412), with 2-(1-methylethoxy)ethanol in male and female rats, the no observed adverse effect concentration (NOAEC) for the chemical was reported to be 130 mg/m³ (30 ppm). Effects observed at higher concentrations ($\geq$430 mg/m³ (100 ppm)) included:

- haemolytic effects;
- increased spleen weights; and
- extramedullary haematopoiesis in the spleen (OECD, 2009; REACH).

Similar effects were observed in a 26-week repeated dose inhalation (whole-body exposure) study in rats. The lowest observed adverse effect concentration (LOAEC) was considered to be 107 mg/m³ (25 ppm). Excessive amounts of haemosiderin in the red and white pulp of the spleen were observed in both sexes at 50 ppm and 200 ppm. Osmotic fragility of the erythrocytes of rats was significantly changed at all doses (25, 50 and 200 ppm). A dose response was observed with changes marked at 200 ppm, slight at 50 ppm and minimal at 25 ppm (ACGIH, 2011; OECD, 2009; REACH).

No toxicologically significant effects were observed in a 26-week repeated dose inhalation (whole-body exposure) study in rabbits, guinea pigs and dogs.

Genotoxicity

In general, monoethylene glycol ethers and their acetates are not genotoxic. The negative results for 2-(1-methylethoxy)ethanol from in vitro studies (bacterial reverse mutation assay and chromosome aberration test), support a conclusion that the chemicals are not genotoxic.

Carcinogenicity

No data are available for the chemicals.

Two carcinogenicity studies in rats and mice (2-year, via inhalation) are available for 2-butoxyethanol (CAS No. 111-76-2). A significant increase in the incidence of liver haemangiosarcomas was seen in male mice, and forestomach tumours were observed in female mice. However, several international reviews of this data (OECD, United States and the European Union) have concluded that the results of these studies are not relevant to humans and that 2-butoxyethanol is not considered a human carcinogen (OECD, 2006; SCHER, 2008).

Based on the proposed mode of actions for the observed tumours (OECD, 2006; SCHER, 2008) and the similar effects observed with the chemicals in acute and chronic toxicity studies, 2-butoxyethanol is considered a suitable analogue for the chemicals being assessed for this endpoint.

Reproductive and Developmental Toxicity

Based on the available data the chemicals are considered not to cause reproductive or developmental toxicity.

Although certain short-chain monoethylene glycol ethers such as 2-methoxyethanol (CAS No. 109-86-4) are known to cause reproductive toxicity, the ability of the glycols to cause testicular toxicity decreases with increasing chain length.

No reproductive or developmental effects were noted in a reproductive and developmental toxicity screening test (OECD TG 421) in rats exposed to2-(1-methylethoxy)ethanol through oral exposure. The NOAEL for reproductive and developmental effects was 125 mg/kg bw/day (top dose tested).

Risk Characterisation

Critical Health Effects

The critical health effects, for risk assessment are acute toxicity via the dermal route of exposure and eye irritation.

Although the chemical, 2-(1-methylethoxy)ethanol, is also reported to cause haemolysis and associated organ toxicity in rats, the severity of effects differs markedly between species. It is considered likely that, similar to 2-butoxyethanol, humans are likely to be the least sensitive. Modelled data demonstrate that even at saturated concentrations of 2-butoxyethanol (a similar haemolytic agent), it is not possible to reach haemolytic blood concentrations of the relevant metabolite in humans by inhalation exposure (NICNAS, 1996; OECD, 2006).

Public Risk Characterisation

The chemicals are currently listed on Schedule 6 of the SUSMP for preparations containing more than 10 %. At concentrations greater than 10 % a number of first aid instructions and safety directions relating to skin and eye contact apply.

Based on information on use of the chemicals internationally, the chemicals are not likely to be widely available for domestic use. Hence, the public risk from these chemicals is not considered to be unreasonable and further risk management is not considered necessary for public safety. However, a modification to the entry in the SUSMP may be appropriate (refer to **Recommendation Section**).

Occupational Risk Characterisation

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

Given the critical systemic long-term, systemic acute, and local health effects, the chemicals may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The chemicals

should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU), e.g. employer, at a workplace, has adequate information to determine appropriate controls.

Based on the available data, the hazard classification in HSIS is considered appropriate for 2-(1-methylethoxy)ethanol. However, the data available support an amendment to the hazard classification in HSIS for 2-(1-methylethoxy)ethyl acetate (refer to **Recommendation section**).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification for 2-(1-methylethoxy)ethyl acetate 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. Current risk management measures are considered adequate for the protection of public health and workers. However, a modified entry in the SUSMP for the specific chemical may be appropriate, as explained below.

Regulatory Control

Public Health

Further risk management is not considered necessary for public safety. However, a modification to the entry in the SUSMP may be appropriate. Consideration should be given to the following:

- whilst the chemicals meet the acute toxicity criteria for Schedule 6, a higher concentration cut off (than the current 10 %) may be appropriate;
- at present, the chemicals falls within the scope of the listing of ethylene glycol monoalkyl ethers in Schedule 6 of the SUSMP for preparations containing more than 10 % glycol ether. However, the health effects of the members of this class of chemicals vary significantly and a separate listing may be more appropriate; and
- any review of the entry in the SUSMP should form part of a review of the entries for all ethylene glycol monoalkylethers and their acetates.

Work Health and Safety

The chemicals are recommended for classification and labelling under the current approved criteria and adopted GHS as below. The acute toxicity classifications apply to both chemicals assessed in this group and are existing classifications for 2-(1-methylethoxy)ethanol. The irritation classification is considered only appropriate for 2-(1-methylethoxy)ethanol. This does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful in contact with skin (Xn; R21) Harmful by inhalation (Xn; R20)	Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)*	Causes serious eye irritation - Cat. 2A (H319)

[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 consumers

Products containing the chemical should be used according to label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular and inhalation exposure to the chemical 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 chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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 chemical.

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 assist with meeting 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 chemical 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 the chemical has not been undertaken as part of this assessment.

References

ACGIH (American Conference of Governmental Industrial Hygienists). Documentation of the Threshold Limit Values for Chemical Substances, ACGIH Signature Publications, 7th Edition, 2011.

Galleria Chemica. Accessed May 2013 at **http://jr.chemwatch.net/galleria/**

National Industrial Chemical Notification and Assessment Scheme (NICNAS a). Human health assessment for ethanol, 2-propoxy. CAS registry number: 2807-30-9. Australian Government Department of Health and Ageing. Accessed May 2013 at **http://www.nicnas.gov.au**

National Industrial Chemical Notification and Assessment Scheme (NICNASb). Human health assessment for ethanol, 2-butoxy-,acetate. CAS registry number: 112-07-2. Australian Government Department of Health and Ageing. Accessed May 2013 at **http://www.nicnas.gov.au**

NICNAS Priority Existing Chemical Report for 2-butoxyethanol (1996) Electronic version for the web, accessed May 2013 at **www.nicnas.gov.au**.

OECD 2006. SIAR category assessment for monoethylene glycol ethers. Accessed October 2012 at **http://webnet.oecd.org/hpv/UI/handler.axd?id=c0edaa0e-2885-4ebe-a102-135ed2bc2da3**

OECD 2009. SIAP& SIDS on 2-(1-methyletoxy)ethanol (109-59-1). Accessed May 2013 at **http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?Key=bc5c93e3-f52b-41e4-8183-cb991adf1cc1&idx=0**

REACH Dossier. 2-(1-methylethoxy)ethanol (109-59-1). Accessed May 2013 at **http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances**

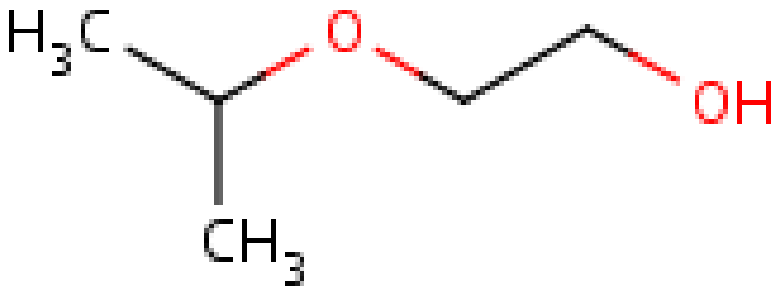
Scientific Committee on Health and Environmental Risks (SCHER)March 2008. Scientific opinion on the risk assessment report on 2-butoxyethanol (EGBE), human health part, CAS 111-76-2 Assessed May 2013 at **http://ec.europa.eu/health/archive/ph_risk/committees/04_scher/docs/scher_o_087.pdf**

Substances in Preparations in Nordic Countries (SPIN). Accessed May 2013 at **http://fmp.spin2000.net**

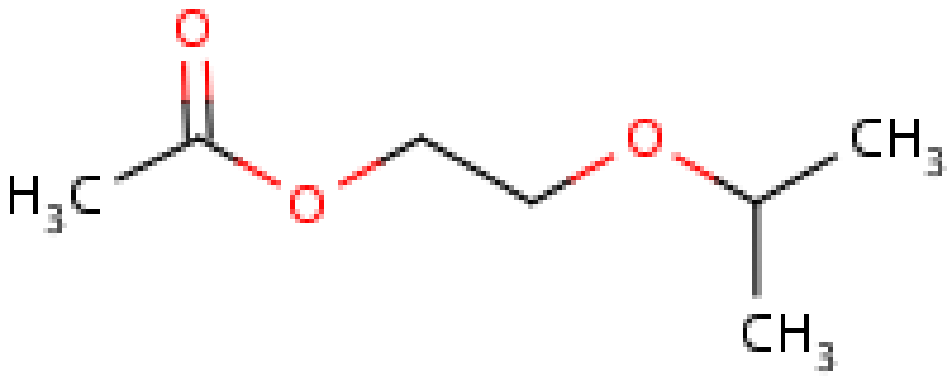
Last Update 28 June 2013

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Ethanol, 2-(1-methylethoxy)-** 2-Isopropoxyethanol Ethylene glycol monoisopropyl ether Isopropyl Cellosolve Isopropyl Oxitol
CAS Number	109-59-1
Structural Formula	

	
Molecular Formula	C5H12O2
Molecular Weight	104.15

Chemical Name in the Inventory and Synonyms	**Ethanol, 2-(1-methylethoxy)-, acetate** 2-(1-Methylethoxy)ethyl acetate Ethanol, 2-(1-methylethoxy)-, acetate Ethanol, 2-isopropoxy-, acetate Ethylene glycol monoisopropyl ether acetate
CAS Number	19234-20-9
Structural Formula	

	
Molecular Formula	C7H14O3
Molecular Weight	146.18

Share this page