Oxalate esters (C1-C4): Human health tier II assessment

18 September 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Ethanedioic acid, diethyl ester	95-92-1
Ethanedioic acid, dibutyl ester	2050-60-4
Ethanedioic acid, dimethyl ester	553-90-2

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

Chemicals in this group are esters of oxalic acid and have similar absorption, metabolism, distribution, and excretion patterns. Given the close structural similarities of the chemicals in this group and their similar molecular weights, they are all expected to have essentially similar physicochemical properties.

Following absorption by oral, dermal and inhalation routes, the chemicals in this group are rapidly metabolised to the parent alcohol and oxalate anion, which exist in the human body as major intermediates in metabolic processes. The data available (see the **Health hazards** section) indicate that the oxalate anion is considered the main moiety responsible for systemic toxicity. Considering that oxalate esters and oxalic acid have similar bioaccessibility and bioavailability in biological fluids, data available for oxalic acid (or its salts) can be 'read across' when data are lacking for the chemicals in this group for systemic toxicity.

Most of the chemicals in this group have similar end uses.

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening

Information Dataset Initial Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemicals are included in the CosIng database with the identified functions of chelating, hair conditioning, masking, plasticisers and solvents.

The chemicals are included in the US Personal Care Products Council's INCI dictionary with the identified functions of fragrance ingredients, plasticisers and solvents. However, there is currently no documented use of the chemicals (Personal Care Products Council, 2011).

The chemicals have reported domestic use including in:

- adhesives, binding agents;
- paints, lacquers and varnishes; and
- sealants.

Available North American databases do not give evidence for use of these chemicals in consumer products, indicating that the chemicals are not likely to be widely available for domestic uses.

The chemicals have reported commercial use including as:

- process regulators; and
- solvents for cellulose esters and ethers, perfumes, natural resins and lacquers.

The chemicals have reported site-limited use including as an intermediate.

The following non-industrial uses have been identified internationally for the chemicals:

- pesticides;
- agricultural;
- flavouring; and
- pharmaceuticals.

Restrictions

Australian

No known restrictions have been identified.

Oxalic acid and its salts are listed in the *Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons 2013* —SUSMP) in Schedule 6. This entry excludes the derivatives and insoluble salts and therefore, the chemicals in this group are not covered by this entry (SUSMP, 2013).

International

The chemicals (as oxalic acid, its esters and alkaline salts) are listed on the following (Galleria Chemica):

- ASEAN Cosmetic Directive Annex III—Part 1 (List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down);
- EU Regulation (EC) No 1223/2009 Annex III (List of substances which cosmetic products must not contain except subject to the restrictions laid down); and
- New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1 (Components cosmetic products must not contain except subject to the restrictions and conditions laid down).

For the above, the chemicals are restricted to use in hair products, for professional use only, at a maximum concentration of 5 %.

Existing Worker Health and Safety Controls

Hazard Classification

The chemical, ethanedioic acid, diethyl ester (CAS No. 95-92-1) is classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xn: R22 (Acute oral toxicity)

Xi: R36 (Irritating to eyes)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 0.5 mg/m^3 (time weighted average, TWA) and 3 mg/m^3 (short-term exposure limit, STEL) has been identified for ethanedioic acid, diethyl ester (CAS No. 95-92-1) in different countries such as Latvia and Finland.

Health Hazard Information

Limited data are available for the chemicals in this group. The chemicals are hydrolysed in the body to form the parent alcohol and oxalate anion. Therefore, where available, data from the parent alcohols and oxalic acid and its salts are considered as suitable analogues for systemic effects, particularly for longer-term toxicity.

Toxicokinetics

Following absorption by oral, dermal and inhalation routes, the chemicals in this group are rapidly metabolised to the parent alcohol and oxalate anion, which exist in the human body as major intermediates in metabolic processes. The hydrolysis of diethyl oxalate (CAS No. 95-92-1) is fast with a $t_{1/2}$ (half-life) of approximately 0.5 day (pH4, 35 °C). The data available indicate that the oxalate anion is the main moiety responsible for systemic toxicity.

Oxalic acid is an organic acid that occurs naturally in food (e.g. spinach, rhubarb, coffee, chocolate, tea etc.). Dietary intake is reported to be 5–500 mg daily, with intake sometimes exceeding 1 g/day. Oxalic acid is also produced endogenously in the normal human body as an end product of the metabolism of glycine, glycolate and ascorbic acid. Endogenous sources constitute 30–70 % (20–30 mg) of the oxalic acid excreted daily. Oxalic acid is reported to be rapidly cleared from the plasma pool. Oxalate absorption in rats and humans ranges from 2–30 % and mainly occurs in the small and large intestine. Oxalic acid is mainly excreted unchanged in the urine as the parent compound or as calcium oxalate. Degradation by intestinal bacteria to CO_2 can occur (NICNASa).

Acute Toxicity

Oral

Based on the available data for one of the chemicals in this group and the analogue chemical (oxalic acid), oral exposure to the chemicals in this group is considered to be acutely toxic.

The chemical, diethyl oxalate (CAS No. 95-92-1) is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). The available data in rats (median lethal dose—LD50 of 400 mg/kg bw) support this classification. Reported signs of toxicity included disturbed respiration, muscle twitching, kidney damage, and central nervous system effects (REACH).

The available data for oxalic acid (LD50 of 425 mg/kg bw) support this classification for the chemicals in the group (NICNASa).

Dermal

Limited data are available for the chemicals in this group. The chemical, diethyl oxalate (CAS No. 95-92-1) has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in rats is >2000 mg/kg bw. Toxic effects in the kidneys (urolithiasis and interstitial inflammation) were observed (REACH).

Inhalation

No data are available.

Corrosion / Irritation

Respiratory Irritation

No data are available.

Skin Irritation

Limited data are available for the chemicals in this group. Based on a positive result reported in a valid and accepted in vitro skin corrosion test for one of the chemicals in this group, classification is warranted (refer to the **Recommendation** section).

The chemical, diethyl oxalate (CAS No. 95-92-1) was shown to have a corrosive effect (based on the cell viability) in a human epidermal EpiDerm^{TM} model when the chemical was left on for one hour. Cell viability relative to the negative control was 9.4 % for the 60-minute treatment (89.5 % for the three-minute treatment) (REACH). The chemical has been reported to be a strong irritant to skin and mucous membranes (HSDB).

Eye Irritation

The potential to cause severe eye damage is implicit within the proposed classification for corrosion. Therefore, it is recommended that the current R36 classification is removed.

Sensitisation

Skin Sensitisation

Although limited data are available on the skin sensitisation potential of these chemicals, based on available information, the chemicals in this group are not considered to be skin sensitisers.

The chemical, diethyl oxalate (CAS No. 95-92-1) in a maximum 30 % solution did not elicit any skin reaction in a mouse local lymph node assay (LLNA) (REACH).

Repeated Dose Toxicity

Oral

The alcohol metabolites, which are produced rapidly under repeated dose conditions, did not cause any significant adverse effects following repeated oral exposure, except at high doses (NICNASb; NICNASc; NICNASd). The oxalate anion is the main moiety responsible for systemic toxicity.

The toxicity of oxalic acid is believed to be due to its ability to chelate free calcium ions, upsetting the calcium-potassium ratio in tissues and, ultimately, causing precipitation as calcium oxalate crystals. Based on the weight of evidence from the available studies for one of the chemicals in the group and the analogue chemical (oxalic acid), the chemicals in this group are likely to cause adverse health effects by accumulation (as calcium oxalate crystals) in the renal tubules causing nephrotoxicity, and accumulation in the testes, which could be linked to impaired sperm quality (refer to the **Reproductive and developmental toxicity** section). Based on these effects, the chemicals are recommended for classification (refer to the **Recommendation** section).

In a 28-day repeated dose oral (gavage) toxicity study (OECD Test Guideline (TG) 407) using ethanedioic acid, diethyl ester (CAS No. 95-92-1) on Wistar Han rats, a no observed adverse effect level (NOAEL) of 20 mg/kg/day was established on the basis of haematological, biochemical and histopathological changes, specifically for effects seen in kidneys. The treatment resulted in significant changes in haematological (haematocrit, haemoglobin, total erythrocyte count) and biochemical parameters (urea, creatinine, albumin). Water consumption was increased in treated animals and urinalysis demonstrated effects of the chemical on urine (pH, presence of leucocytes and protein). The chemical had a significant effect on biometry and kidney structure (increased weight and oxalate nephrolithiasis at the mid to highest dose levels tested). The severity of effects increased with exposure with slight to mild oxalate nephrolithiasis observed in animals exposed to 60 mg/kg bw/day and severe nephrolithiasis observed in animals exposed to 180 mg/kg bw/day (REACH).

Similar kidney toxicity effects were observed with oxalic acid, albeit at higher doses (NICNASa).

Dermal

No data are available for the chemicals in this group.

Inhalation

No data are available for the chemicals in this group.

Observation in humans

The chemicals are expected to rapidly metabolise to oxalic acid. Prolonged exposure to oxalic acid may lead to urinary stones as crystals of calcium oxalate which are a major constituent of kidney stones (HSBD).

Genotoxicity

Based on the weight of evidence from the available studies for one of the chemicals in the group and the metabolite chemicals, the chemicals in this group are not considered to be genotoxic.

Diethyl oxalate (CAS No. 95-92-1) was negative in reverse mutation assays using *Salmonella typhimurium* with and without metabolic activation. The chemical was also reported negative in an in vitro mouse lymphoma (L5178Y TK+/-) forward mutation assay (MLA) and in peripheral blood lymphocytes in an in vitro micronucleus test (MN test) with and without metabolic activation (REACH). No in vivo test assays are available.

The rapidly produced metabolites (oxalate ion and parent alcohols) are not considered to be genotoxic (NICNASa; NICNASb; NICNASc, NICNASd).

Carcinogenicity

No data are available for the chemicals in this group.

Data available for the rapidly produced metabolites (oxalate anion and parent alcohols) indicate that these chemicals are not likely to be carcinogenic (NICNASa; NICNASb; NICNASc; NICNASd). Whilst exposure to ethanol (CAS No: 64-17-5) from consuming alcoholic beverages is associated with an increased risk of carcinogenicity, the increased risk is dose-dependent and is not considered applicable at doses relevant to occupational exposure and use of consumer products containing ethanol (NICNASd), or by implication, diethyl oxalate.

Reproductive and Developmental Toxicity

Limited data are available for the chemicals. Based on the weight of evidence from the available studies for one of the chemicals in the group and the metabolite chemicals, the chemicals in this group are not considered to cause reproductive or developmental toxicity. Any reproductive and developmental effects are considered secondary to parental toxicity.

In a reproduction/developmental toxicity study (OECD TG 421), Wistar Han rats were exposed to ethanedioic acid, diethyl ester (CAS No. 95-92-1) by gavage. The animals were administered 30, 90 and 270 mg/kg/day for the duration of the study. One female died at the highest dose. Changes in growth and food consumption were seen at all dose levels in parental males and females. In the parental males, the kidneys were enlarged with changed colour and structure at the middle and highest dose levels. Histopathological examination revealed mild oxalate nephrolithiasis in males at the middle dose level. Marked oxalate nephrolithiasis was seen at the highest dose level, accompanied by changes to lymphatic organs and the stomach. Males had decreased prostate and testicular weights at the middle and highest dose levels. Histopathological examination of parental male reproductive systems showed a high incidence of effects at the highest dose level (various types of damage to spermatogenesis and oxalate crystals in testes). At the middle dose level, degenerated spermatids and vacuolated Sertoli-like cells were observed in two males. Sperm motility and sperm morphology were impaired in treated males at the middle and the highest dose levels. In the females, a decrease in the mating index and an increased occurrence of pre-implantation and post-implantation loss were detected. The number of pups, average weight of the litter and average pup body weight were decreased at the middle and highest dose levels. These negative effects were also marked at the highest dose level. A NOAEL of 30 mg/kg/day was established (REACH).

Similar effects were observed with oxalic acid (NICNASa).

The parent alcohol metabolites are not considered to cause any specific reproductive or developmental toxicity in animals, or have reproductive or developmental toxicity in humans (NICNASb; NICNASc; NICNASd). Whilst exposure to ethanol (CAS No: 64-17-5) from consuming alcoholic beverages is associated with an increased risk of reproductive and developmental toxicity,

the increased risk is dose-dependent and not considered applicable at doses relevant to occupational exposure and using consumer products containing ethanol (NICNASd), or by implication, diethyl oxalate.

Risk Characterisation

Critical Health Effects

The critical health effects for risk assessment are systemic acute effects from oral exposure and local effects (corrosion). The chemicals can also cause harmful cumulative effects following repeated exposure.

Public Risk Characterisation

International information indicates that the chemicals are not likely to be widely available for domestic and cosmetic use. Hence, the public risk from these chemicals is not considered to be unreasonable.

Although oxalic acid and its salts are listed in the SUSMP in Schedule 6, this entry does not include derivatives and insoluble salts (SUSMP, 2013). Given the comparable toxicity of these chemicals to oxalic acid, additional regulatory controls could be required should information become available to indicate that the chemicals are used in domestic and cosmetic products in Australia.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to the chemicals can 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 might 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 acute, cumulative and local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise oral and dermal exposure to the chemicals 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 appropriate controls.

The available data support an amendment to the hazard classification in HSIS (refer to the **Recommendation** section).

NICNAS Recommendation

The assessment of the chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety as adopted by the relevant state or territory. No further assessment is required unless information becomes available to indicate that the chemicals are used in domestic and cosmetic products in Australia.

Regulatory Control

Work Health and Safety

The chemicals are recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards. Note: The potential to cause severe eye damage is implicit within the proposed corrosivity classification. Therefore it is recommended that the current R36 classification for ethanedioic acid, diethyl ester is removed.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)*	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage - Cat. 1B (H314)
Repeat Dose Toxicity	Danger of cumulative effects (R33)	May cause damage to organs (kidney) through prolonged or repeated exposure - Cat. 2 (H373)

[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 chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral/dermal exposure to the chemical(s) 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 closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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

Hazardous Substances Data Bank (HSDB). National Library of Medicine. Accessed June 2014 at **http://toxnet.nlm.nih.gov**.

Hazardous Substances Information System (HSIS). Safe Work Australia. Available: **http://hsis.safeworkaustralia.gov.au/HazardousSubstance**

National Industrial Chemicals Notification and Assessment Scheme (NICNAS d). Inventory Multi-Tiered and Prioritisation (IMAP): Human Health Tier II Assessment for ethanol (Cas No. 64-17-5). Accessed August 2014 at **http://www.nicnas.gov.au**

National Industrial Chemicals Notification and Assessment Scheme (NICNASa). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for Oxalic acid. Accessed August 2014 at **http://www.nicnas.gov.au**

National Industrial Chemicals Notification and Assessment Scheme (NICNASb). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for Methanol (CAS No. 67-56-1). Accessed August 2014 at **http://www.nicnas.gov.au**

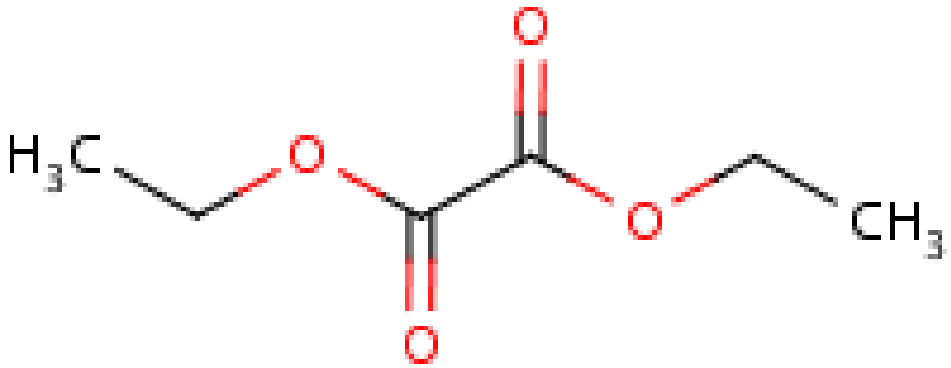
National Industrial Chemicals Notification and Assessment Scheme (NICNASc). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for 1-Butanol (CAS No. 71-36-3). Accessed August 2014 at **http://www.nicnas.gov.au**

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossiers. Available: **http://echa.europa.eu/information-on-chemicals/registered-substances**

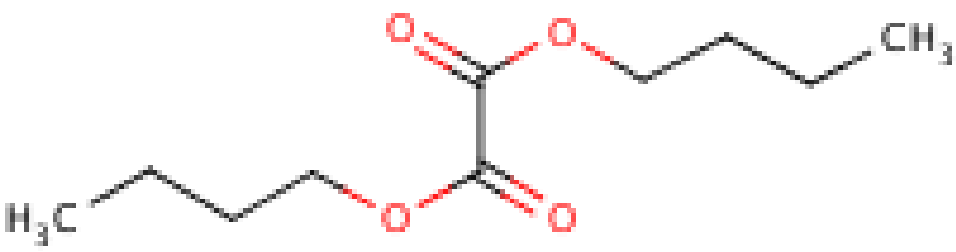
Last Update 18 September 2014

Chemical Identities

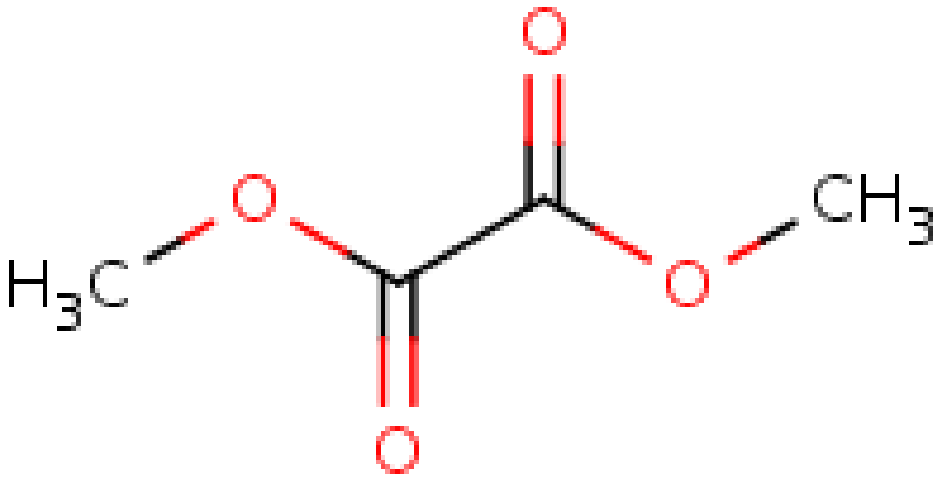
Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, diethyl ester** Ethyl oxalate Diethyl oxalate Diethyl ethanedioate
CAS Number	95-92-1
Structural Formula	

	
Molecular Formula	C6H10O4
Molecular Weight	146.14

Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, dibutyl ester** Oxalic acid, dibutyl ester Butyl oxalate Dibutyl oxalate
CAS Number	2050-60-4
Structural Formula	

	
Molecular Formula	C10H18O4
Molecular Weight	202.25

Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, dimethyl ester** Dimethyl oxalate Methyl oxalate
CAS Number	553-90-2
Structural Formula	

	
Molecular Formula	C4H6O4
Molecular Weight	118.1

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