Oxalic acid soluble salts: Human health tier II assessment

18 September 2014

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Ethanedioic acid, disodium salt	62-76-0
Ethanedioic acid, monopotassium salt	127-95-7
Ethanedioic acid, potassium salt (2:1)	127-96-8
Ethanedioic acid, dipotassium salt	583-52-8
Ethanedioic acid, diammonium salt	1113-38-8
Ethanedioic acid, monosodium salt	1186-49-8
Ethanedioic acid, diammonium salt, monohydrate	6009-70-7
Ethanedioic acid, potassium salt (2:1), dihydrate	6100-20-5
Ethanedioic acid, dipotassium salt, monohydrate	6487-48-5
Ethanedioic acid, potassium salt	10043-22-8

Chemical Name in the Inventory	CAS Number
Ethanedioic acid, ammonium salt	14258-49-2

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 soluble salts 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 rapidly dissociate to the oxalate anion and the respective metallic cations (ammonium, potassium and sodium, all of which have low toxicity). Oxalate exists in the human body as a major intermediate in metabolic processes. The data available indicate that the oxalate anion is the main moiety responsible for systemic toxicity (NICNASa; NICNASb). Considering that oxalate esters and oxalic acid have similar bioaccessibility and bioavailability in biological fluids to oxalate salts, data available for oxalic acid and its esters 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; 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 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 and anticorrosive.

The chemicals are included in the US Personal Care Products Council's INCI dictionary with the identified functions of buffering and corrosion inhibitors. However, there are currently no documented uses of the chemicals in the United States (Personal Care Products Council, 2011).

The chemicals have reported domestic use including in:

- paints, lacquers and varnishes; and
- surface treatments.

Only ammonium oxalate (CAS No. 14258-49-2) was identified in the Household Products database (autoproducts, 1-10%) indicating that the chemicals are not likely to be widely available for domestic uses.

Restrictions

Australian

The chemicals are soluble salts of oxalic acid and fall within the scope of the listing of oxalic acid 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 of oxalic acid (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 chemicals (under "salts of oxalic acid with the exception of those specified elsewhere in Hazardous Substances Information System (HSIS))" are classified as hazardous in HSIS as:

Xn; R21/22 (acute toxicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit of 3 mg/m^3 (1 ppm) short-term exposure limit (STEL) has been identified for ethanedioic acid, disodium salt (CAS No. 62-76-0) in Finland.

Health Hazard Information

Limited data are available for the chemicals in this group. The chemicals are dissociated in the body to form oxalate anion. Therefore, where available, data from oxalic acid and its esters are considered as suitable analogues for systemic effects.

Toxicokinetics

Following absorption by oral, dermal and inhalation routes, the chemicals in this group are rapidly dissociated to the oxalate anion, which exists in the human body as a major intermediate in metabolic processes. 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 (eg 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

The chemicals are classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). No data were available for the chemicals in this group. The available data on oxalic acid (median lethal dose—LD50 of 425 mg/kg bw) support this classification. Reported signs of toxicity included disturbed respiration, muscle twitching, kidney damage, and central nervous system effects (NICNASa).

Dermal

The chemicals are classified as hazardous with the risk phrase 'Harmful in contact with skin' (Xn:R21) in HSIS (Safe Work Australia). No data were available for the chemicals in this group. While the available animal data on oxalic acid does not support this classification, in the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend this classification.

Oxalic acid had low toxicity in rabbits following dermal exposure. There were mortalities in three rabbits topically administered 20000 mg/kg bw of the chemical (NICNASa).

Inhalation

No data are available.

Corrosion / Irritation

Respiratory Irritation

Based on reported effects following inhalation exposure, the chemical is considered to be irritant to the respiratory tract and a classfication is warranted.

Inhalation of soluble oxalates may produce irritation of the respiratory tract. Reported local effects included ulceration of the mucous membranes and cough (SDS).

To test respiratory mucosal irritation, Calu-3 cells were treated with sodium oxalate (0.2% (w/v) for 60 min). The viability was decreased to 65% (Ihekwereme et al., 2014).

Skin Irritation

No data are available for the chemicals in this group. Based on positive results reported for eye irritation for the chemicals and corrosive properties of oxalic acid and oxalic acid esters (NICNASa; NICNASb), skin irritant effects cannot be ruled out. Numerous safety data sheets for the chemicals indicate the potential for skin corrosion/irritation. Chemicals in this group vary in pK_a, from the basic dipotassium and disodium salts, to approximately neutral monosodium and monopotassium salts, and somewhat acidic ethanedioic acid, potassium salt (2:1). Due to this variation, it is not possible to predict the irritation potential of

the entire group. If data on the irritation potential or pH are available for the individual group members, this may be used to give individual classifications.

Eye Irritation

Based on the available data the chemicals are considered to cause severe eye damage and a classification is warranted (refer to the **Recommendation** section).

The chemical (sodium oxalate) has been reported as a severe eye irritant (corneal opacity score=4; iris score=2) (ICCVAM, 2006).

In a two-tiered testing strategy using the EpiOcular Eye Irritation Test combined with the Bovine Corneal Opacity and Permeability (BCOP test), the chemical (sodium oxalate) was found to be severely to moderately irritating (Kolle et al., 2011).

While there may be some difference associated with the range of pK_a values in this group, the commonality of high eye damage potential between sodium oxalate, oxalic acid and oxalate esters indicates that a common non-pH dependent mechanism applies.

Sensitisation

Skin Sensitisation

No data are available on the skin sensitisation potential of these chemicals. Based on available information on the analogue chemicals (oxalic acid and its esters), the chemicals in this group are not considered to be sensitisers (NICNASa; NICNASb). Classification is not warranted.

Repeated Dose Toxicity

Oral

No data are available for the chemicals. The oxalate anion is the main moiety responsible for systemic toxicity. Based on the weight of evidence from the available studies for the analogue chemicals (oxalic acid and its esters), the chemicals in this group are likely to cause adverse health effects by accumulation of the chemical (as calcium oxalate crystals) in the renal tubules causing nephrotoxicity, and accumulation in the testes which could be linked to impaired sperm quality (NICNASa; NICNASb). Based on these effects, the chemicals are recommended for classification (refer to the **Recommendation** section).

Dermal

No repeat dose dermal toxicity data are available.

Inhalation

No repeat dose inhalation toxicity data are available.

Genotoxicity

No data are available for the chemicals in this group. Based on the weight of evidence from the available study for the analogue chemicals (oxalic acid and its esters), the chemicals in this group are not likely to be genotoxic.

The analogue chemicals (oxalic acid and its esters) were reported as negative in various in vitro tests including reverse mutation assays using *Salmonella typhimurium* with and without metabolic activation, a chromosome aberration test and a micronucleus test (NICNASa; NICNASb).

Carcinogenicity

No data are available for the chemicals in this group. Based on the weight of evidence from the available study on oxalic acid, the chemicals in this group are not likely to be carcinogenic.

A limited two-year feeding study in rats with oxalic acid gave no evidence of carcinogenicity (NICNASa).

Reproductive and Developmental Toxicity

No data are available for the chemicals in this group. Based on the weight of evidence from the available studies on the analogue chemicals (oxalic acid and its esters), the chemicals in this group are not considered to cause specific reproductive or developmental toxicity.

The analogue chemicals did not show any specific reproductive or developmental toxicity. Any reproductive or developmental toxicity effects were only observed secondary to parental toxicity (NICNASa; NICNASb).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local effects (skin irritation, eye damage and respiratory irritation) and systemic acute and cumulative effects (acute and cumulative toxicity from oral exposure).

Public Risk Characterisation

International information indicates that the chemicals are not likely to be widely available for domestic and cosmetic use.

The chemicals are currently listed in Schedule 6 of the SUSMP. A number of warning statements, first aid instructions and safety directions relating to corrosivity, contact with skin and the breathing of dusts and mists apply.

The current controls are considered adequate to minimise the risk to public health posed by any domestic and cosmetic products containing the chemicals. Therefore, no further risk management is necessary for public safety.

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 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 and cumulative, and local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation 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.

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.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)* Harmful in contact with skin (Xn; R21)*	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41) Irritating to skin (Xi; R38) Irritating to respiratory system (Xi; R37)	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
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/ocular/inhalation 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

Galleria Chemica. Accessed September 2014 at **https://jr.chemwatch.net/galleria/**

Hazardous Substances Data Bank (HSDB). US National Library of Medicine. Available: **http://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm**

ICCVAM 2006. ICCVAM test method evaluation report: Appendix H. Accessed August 2014 at **http://ntp.niehs.nih.gov/iccvam/docs/ocutox_docs/oteval/apph.pdf**

Ihekwereme C, Esimone, C, Shao D, and Agu RU, 2014. Preliminary studies on validation of calu-3 cell line as a model for screening respiratory mucosa irritation and toxicity. Pharmaceutics. 6(2): 268–280. Accessed September 2014 at **http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4085599/**

Kolle SN, Kandarova H, Wareing B, Ravenzwaay B and Landsiedel R 2011. In-house validation of the epiocular™ eye irritation test and its combination with the bovine corneal opacity and permeability test for the assessment of ocular irritation. ATLA 39(4), 365–387. Accessed August 2014 at **http://www.ncbi.nlm.nih.gov/pubmed/21942548**

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 Oxalate esters. Accessed August 2014 at **http://www.nicnas.gov.au**

Personal Care Product Council, 2011. Compilation of Ingredients Used in Cosmetics in the United States, 1st Edition.

Personal Care Products Council (INCI Dictionary). Accessed July 2014 at **http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp**

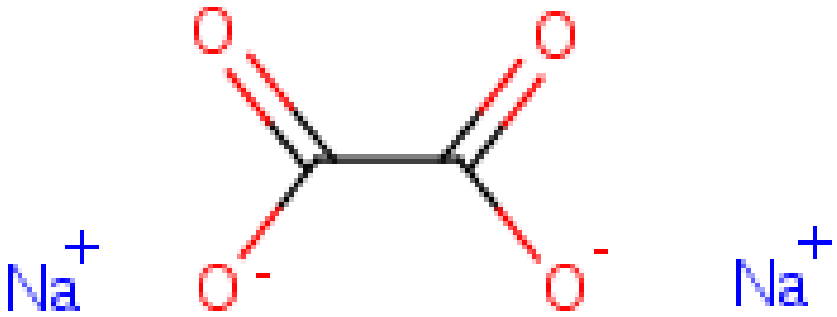
Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed July 2014 at **http://hsis.safeworkaustralia.gov.au/HazardousSubstance**

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2013. Accessed July 2014 at **http://www.comlaw.gov.au/Details/F2013L01607/Download**

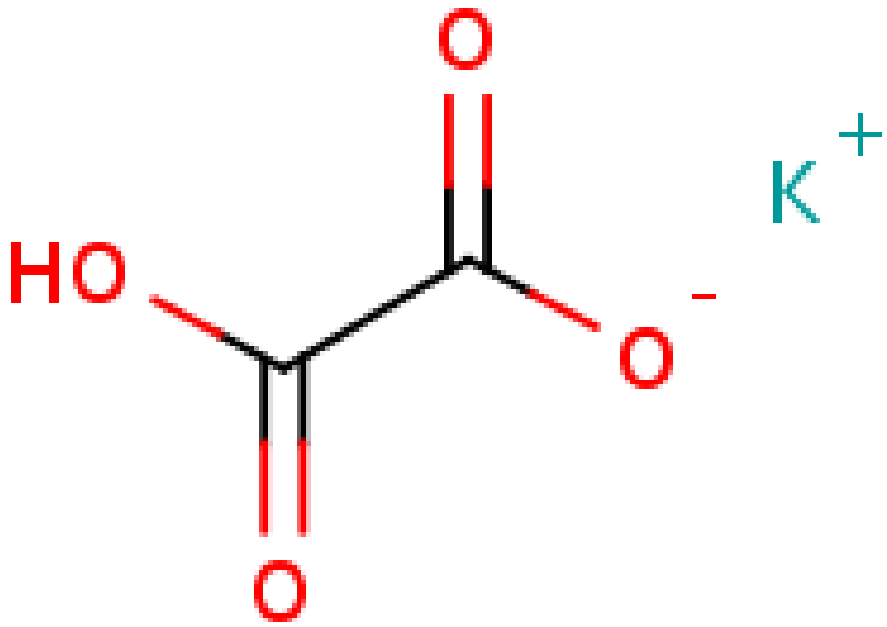
Last Update 18 September 2014

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, disodium salt** Sodium oxalate Disodium oxalate
CAS Number	62-76-0
Structural Formula	

	
Molecular Formula	C2H2O4.2Na
Molecular Weight	134

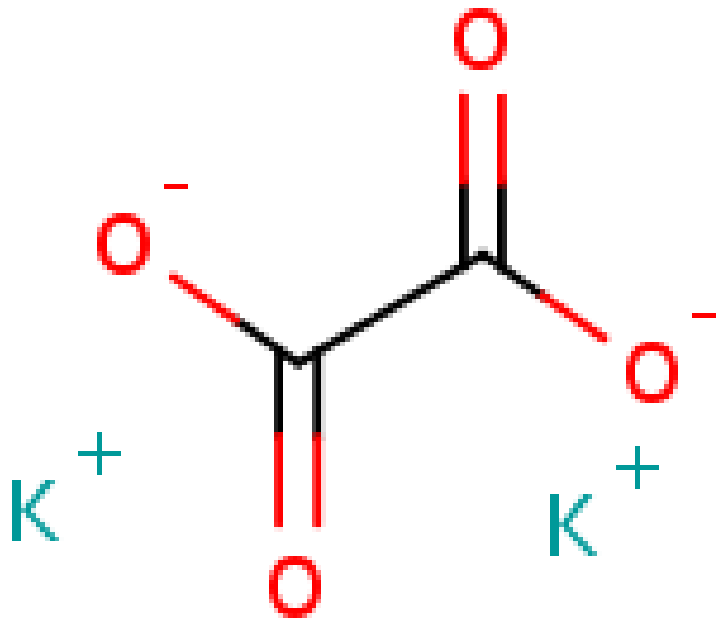
Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, monopotassium salt** Potassium binoxalate Potassium hydrogen oxalate
CAS Number	127-95-7
Structural Formula	

	
Molecular Formula	C2H2O4.K
Molecular Weight	128

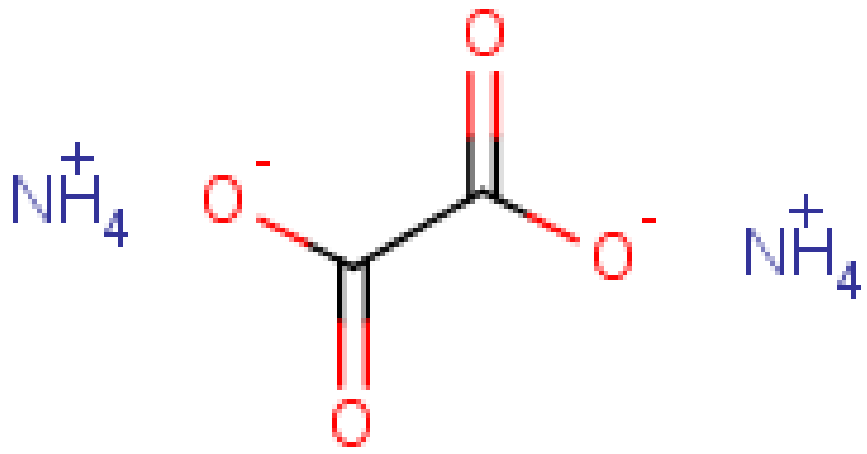
Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, potassium salt (2:1)** Potassium tetroxylate
CAS Number	127-96-8
Structural Formula	

	
Molecular Formula	C2H2O4.1/2K
Molecular Weight	220

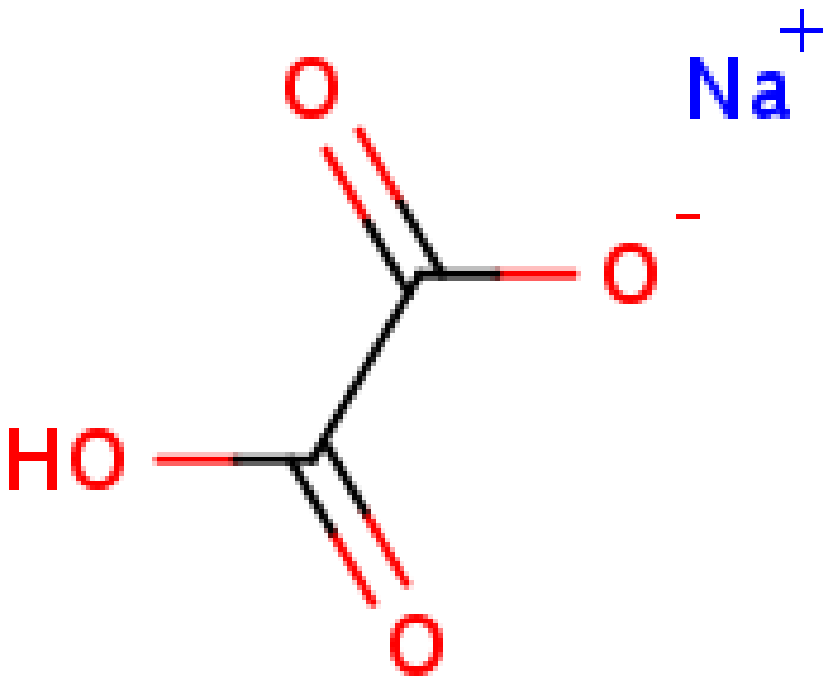
Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, dipotassium salt** Potassium oxalate Ethanedioic acid, potassium salt (1:2) Potassium neutral oxalate
CAS Number	583-52-8
Structural Formula	

	
Molecular Formula	C2H2O4.2K
Molecular Weight	166.2

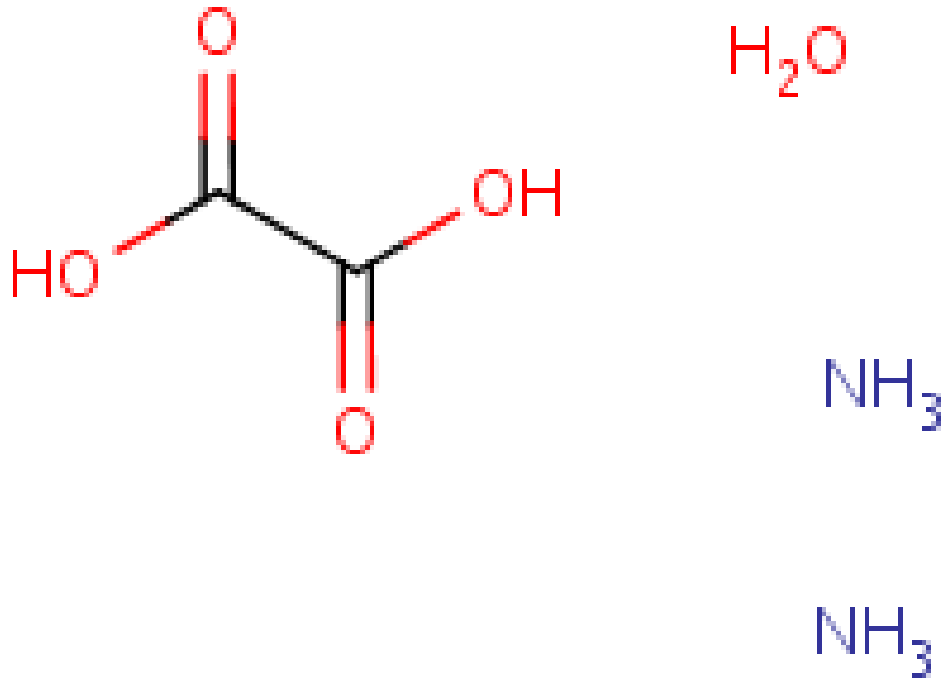
Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, diammonium salt** Ammonium oxalate
CAS Number	1113-38-8
Structural Formula	

	
Molecular Formula	C2H2O4.2H3N
Molecular Weight	124

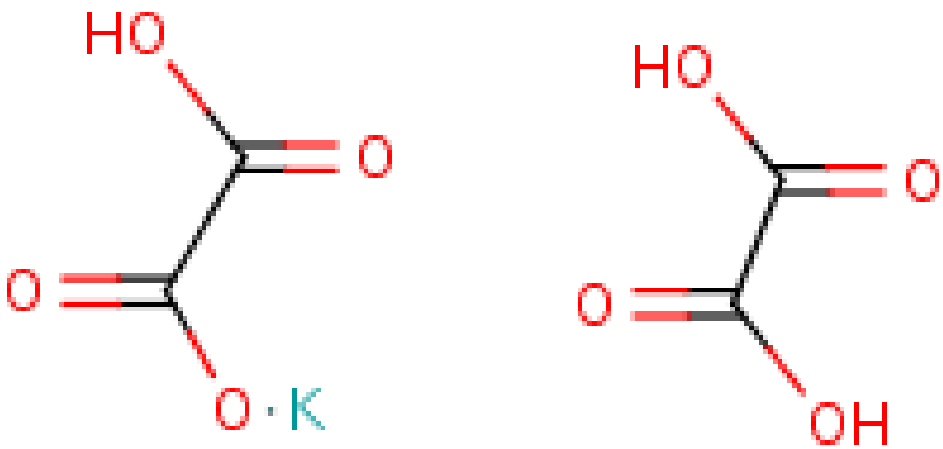
Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, monosodium salt** Sodium hydrogen oxalate
CAS Number	1186-49-8
Structural Formula	

	
Molecular Formula	C2H2O4.Na
Molecular Weight	112

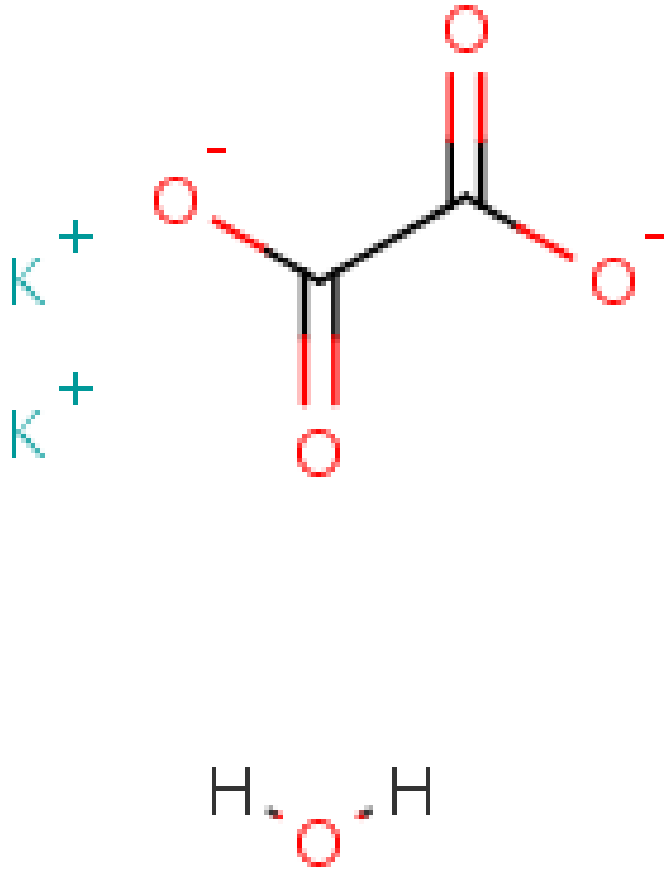
Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, diammonium salt, monohydrate** Oxalic acid, diammonium salt, monohydrate Ammonium oxalate monohydrate
CAS Number	6009-70-7
Structural Formula	

	
Molecular Formula	C2H2O4.2H3N.H2O
Molecular Weight	142.1

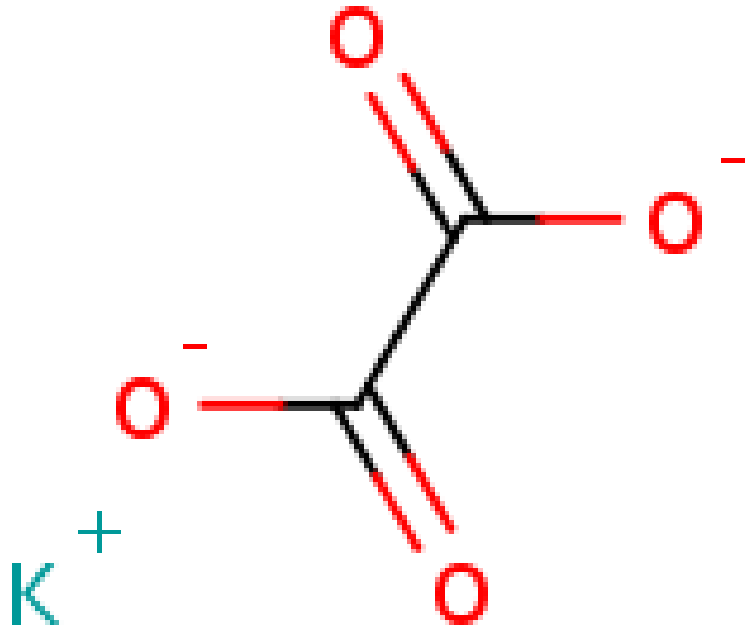
Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, potassium salt (2:1), dihydrate** Oxalic acid, potassium salt (2:1), dihydrate Potassium oxalate (KH3(C2O4)2), dihydrate Potassium trihydrogen dioxalate dihydrate
CAS Number	6100-20-5
Structural Formula	

	
Molecular Formula	C2H2O4.H2O.1/2K
Molecular Weight	218.2

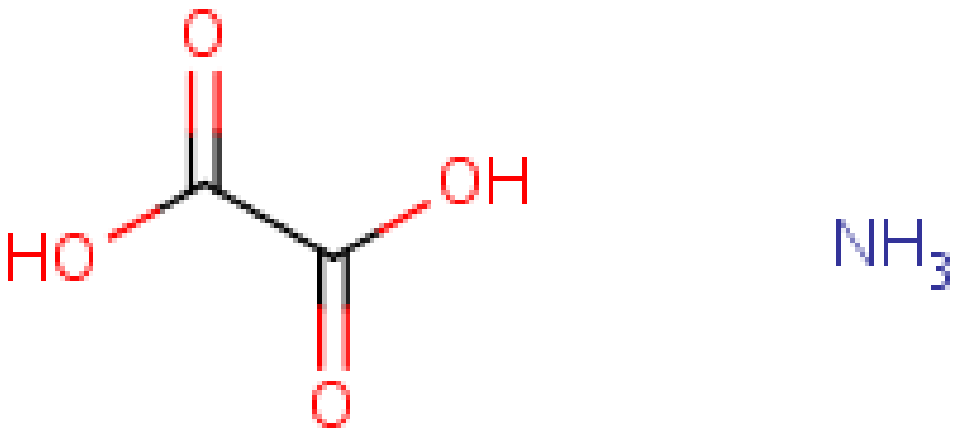
Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, dipotassium salt, monohydrate** Dipotassium oxalate, monohydrate Oxalic acid, dipotassium salt, monohydrate
CAS Number	6487-48-5
Structural Formula	

	
Molecular Formula	C2H2O4.H2O.2K
Molecular Weight	184.2

Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, potassium salt**
CAS Number	10043-22-8
Structural Formula	

	
Molecular Formula	C2H2O4.xK
Molecular Weight	127

Chemical Name in the Inventory and Synonyms	**Ethanedioic acid, ammonium salt** Ammonium oxalate
CAS Number	14258-49-2
Structural Formula	

	
Molecular Formula	C2H2O4.xH3N
Molecular Weight	107.1

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