Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Glyoxylic acid

Evaluation statement

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AICIS evaluation statement

Subject of the evaluation

Glyoxylic acid

Chemicals in this evaluation

Name	CAS registry number
Acetic acid, oxo-	298-12-4
Acetic acid, dihydroxy-	563-96-2

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemicals are listed on the Australian Inventory of Industrial Chemicals (the Inventory).

This evaluation is a human health risk assessment for all identified industrial uses of the chemicals in Australia.

On the Inventory, glyoxylic acid (CAS No. 298-12-4) and its monohydrate (CAS No. 563-96-2) have their own specific chemical identity and CAS number. Both chemicals are available commercially. In aqueous conditions the 2 chemicals are in equilibrium between the anhydrous form (glyoxylic acid), and geminal diol (gem-diol) form (dihydroxyacetic acid) with the equilibrium strongly favouring the gem-diol form. Therefore, these chemicals are considered equivalent for the purposes of this evaluation. The majority of toxicological data exist for glyoxylic acid (CAS No. 298-12-4) 50% w/v in aqueous solution. These data are therefore considered relevant for both chemicals.

Glycolic acid is structurally related to glyoxylic acid and both chemicals have similar physicochemical properties. Glycolic acid is used as a read across in determining the potential for dermal and inhalation absorption of glyoxylic acid and its possible irritation effects to the respiratory system.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of the chemicals in Australia. Based on international use information, the chemicals are used in cosmetics, as:

- semi-permanent hair straightening agents

- buffering agents (pH adjuster) in shampoos, conditioners, lotions and creams
- anti-static agents in (non-colouring) hair products and other hair grooming aids.

Although glyoxylic acid is commonly sold in product formulations containing 50% w/v in aqueous solution, the chemical is reported to be used at concentrations of up to 12% in cosmetic end-use products.

Glyoxylic acid has reported commercial uses as a corrosion inhibitor, pH regulator and anti-scaling agent in the manufacture of cleaning and furnishing products.

It has site-limited uses as intermediate for the manufacture of other substances, manufacture and production of leather tanning, dye or impregnation products and fabricated metal products.

While there are uses as non-agricultural pesticides and preservative in the flavour industry (vanillin production) reported overseas, these are considered non-industrial uses in Australia.

Human health

Summary of health hazards

Based on the available toxicity data of glyoxylic acid (CAS No. 298-12-4), the critical health effects for risk characterisation include local effects (skin sensitisation, eye damage and possible respiratory irritation).

In a local lymph node assay (LLNA) with glyoxylic acid, the estimated concentration to produce a 3-fold increase in lymphocyte proliferation (EC3) was calculated to be 5.05%. The potential for skin sensitisation was supported by phenotype analysis, results from a non-guideline Freund's complete adjuvant test with open challenge and in silico predictions.

The chemicals are not considered to be skin irritants based on an in vivo dermal irritation study (conducted according to OECD TG 404) in rabbits. However, the chemicals are expected to cause serious eye damage based on an in vivo eye irritation study (conducted according to OECD TG 405) in rabbits.

No data are available on local and systemic effects following inhalation exposure.
Based on read across from glycolic acid, the chemical is expected to be readily absorbed following inhalation exposure and may cause respiratory irritation effects.

Both positive and negative results were reported in bacterial reverse mutation assays conducted with glyoxylic acid. Negative results were reported in an in vivo mammalian erythrocyte micronucleus test in CD-1 mice when administered at doses up to 914 mg/kg body weight (bw). Based on the available data, the chemicals are not considered to have genotoxic potential.

Based on the available data the chemicals:

- have low acute and dermal toxicity
- are not expected to cause systemic health effects following repeated oral exposure
- are not expected to cause specific reproductive or developmental toxicity effects.

Hazard classifications relevant for worker health and safety

The chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards. These are the existing classification for glyoxylic acid (CAS No. 298-12-4) (see **Existing Australian regulatory controls: Workers** section).

Health hazards	Hazard category	Hazard statement
Serious eye damage/eye irritation	Eye Damage 1	H318: Causes serious eye damage
Skin sensitisation	Skin Sens. 1B	H317: May cause an allergic skin reaction

The classification should have the following note appended

'Note B: Some substances (acids, bases, etc.) are placed on the market in aqueous solutions at various concentrations. Therefore, these solutions require different classification and labelling since the hazards vary at different concentrations. Entries with Note B have a general designation of the following type: 'nitric acid …%'. In this case the supplier should state the percentage concentration of the solution on the label. Unless otherwise stated, it is assumed that the percentage concentration is calculated on a weight/weight basis.)'

Summary of health risk

Public

Although no use information was available in Australia, the chemicals have known international uses in cosmetic products at end use concentrations up to 12%. The same use concentrations, use patterns, and hence widespread public exposure are expected in Australia.

Based on the available use information, the public may be exposed to these chemicals:

- at concentrations up to 12%
- by direct application of the chemicals to the skin and hair
- by inhaling aerosols/vapours.

Given the identified health hazards (eye damage, skin sensitisation and possible respiratory irritation) the evidence indicates that there is a risk to the public that requires control measures to minimise ocular, dermal and inhalation exposure (see **Proposed means for managing risks** section).

The principal routes of exposure will be dermal and ocular exposure. The risks of eye irritant effects will be dependent on the pH and the concentration of the chemicals in cosmetic products. When the chemical is used as a buffering agent, the concentration of free acid will be reduced and the concentration of the chemical in cosmetic products is expected to be low. However, the chemical has been reported to be used at low pH in hair straightening products. The chemical also has potential to cause sensitisation effects. Therefore, there is risk of skin sensitisation in consumers using the products containing the chemical. Inhalation of aerosols/vapours is expected when the product is applied onto the hair and subsequently heated during hair straightening process. Based on the respiratory absorption and respiratory effects of glycolic acid as read across, the risk of respiratory irritation cannot be ruled out.

Workers

During product formulation, inhalation, ocular and dermal exposure might 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 these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Glyoxylic acid is sold in product formulation as 50% w/v in aqueous solution and up to 12% in hair products for waving and straightening. Dermal exposure may occur when hairdressers apply the products containing the chemical onto the hair. Inhalation of aerosols and vapours of the chemical may also occur during hair straightening process.

Given the critical local health effects (eye damage and skin sensitisation and uncertainty on respiratory irritation), these chemicals could pose a risk to workers. Control measures to minimise inhalation, ocular and dermal exposure are required to manage the risk to workers (see **Proposed means for managing risk** section).

Proposed means for managing risk

Public health

Recommendation to Department of Health and Aged Care

It is recommended that the delegate of the Secretary for Poisons Scheduling lists the chemicals in the *Poisons Standard, the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

It is recommended that to manage the potential risks associated with the use of these chemicals that the entry:

- restricts the concentration of these chemicals in cosmetics
- results in labelling requirements that provides warning statements and safety directions relating to skin sensitisation and eye irritation.

Consideration should be given to the following:

- the potential use of these chemicals in cosmetic products available in Australia at concentrations up to 12%
- the skin sensitisation potential (EC3 value of 5.05%)
- the potential for serious eye damage and potential respiratory irritation particularly in products with low pH (≤0.3).

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety for glyoxylic acid, monohydrate (CAS No. 563-96-2).

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from dermal and ocular exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- using local exhaust ventilation to prevent these chemicals from entering the breathing zone of any worker
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with these chemicals.

Measures required to eliminate or manage risk arising from storing, handling and using these hazardous chemicals depend on the physical form and how these chemicals are used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to these chemicals, if valid techniques are available to monitor the effect on the worker's health

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The conclusions of this evaluation are based on the information described in this Evaluation Statement.

Considering the proposed means of managing risks, the Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the proposed means of managing the risks identified during this evaluation are implemented.

Note: Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.

Supporting information

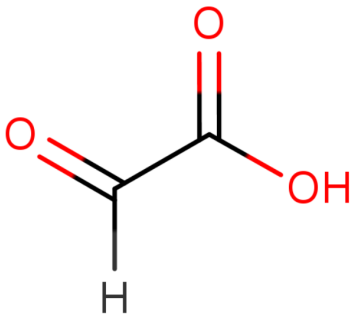
Grouping rationale

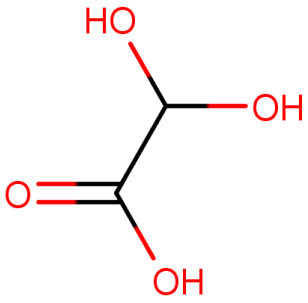
The chemicals in this group, glyoxylic acid and its monohydrate are organic compounds, and are a part of a group of C_2 carboxylic acids. They are reported to be found in plants, and animal tissues. In aqueous conditions the 2 chemicals are in equilibrium between the anhydrous form (glyoxylic acid) and gem-diol form (dihydroxyacetic acid), with the equilibrium strongly favouring the gem-diol form.

On the Inventory, glyoxylic acid and its monohydrate have their own specific chemical identity and CAS number. Both chemicals are available commercially. Whilst most hydrates are regarded as a mixture of the anhydrous form of the chemical and water, this does not apply to covalently bonded hydrates. Due to the ready interconversion, both chemicals are considered equivalent for the purposes of this Evaluation. The majority of toxicological data exist for glyoxylic acid 50% w/v in aqueous solution. As the chemicals exist in equilibrium in aqueous conditions, these data are considered relevant for both chemicals.

Glycolic acid is structurally related to glyoxylic acid and both chemicals have similar physicochemical properties (NICNAS 2000). Glycolic acid is used as a read across in determining the dermal and inhalation absorption of glyoxylic acid and its possible irritation effects to the respiratory system.

Chemical identity

Chemical name	Acetic acid, oxo-
CAS No.	298-12-4
Synonyms	glyoxylic acid (INCI); glyoxalic acid; formylformic acid; and oxoacetic acid
Structural formula	
Molecular formula	C2H2O3
Molecular weight (g/mol)	74.0348
SMILES	OC(=O)C=O
Chemical description	The chemical often exists as the hydrate or cyclic dimer

Chemical name	Acetic acid, dihydroxy-
CAS No.	563-96-2
Synonyms	glyoxylic acid, monohydrate; dihydroxyacetic acid (INCI); 2-oxoacetic acid hydrate; glyoxylic acid hydrate; and oxaldehydic acid hydrate
Structural formula	
Molecular formula	C2H4O4
Molecular weight (g/mol)	92.05
SMILES	OC(O)C(O)=O
Chemical description	-

Relevant physical and chemical properties

The following are physical and chemical properties of glyoxylic acid (CAS No. 298-12-4). No information on physical and chemical properties was available for glyoxylic acid, monohydrate (CAS No. 563-96-2).

Physical form	Colourless to yellowish liquid with pungent odour (as 50% w/v aqueous solution)
Melting point	98 °C at 1013 hPa
Boiling point	111 °C at 1013 hPa
Vapour pressure	1.060 mm Hg at 25 °C
Water solubility	1.00E+06 mg/L at 25 °C
Henry's law constant	2.99E-09 atm-m^3/mole
pKa	3.12 at 25 °C
log K_{ow}	-1.4 at 20 °C

Introduction and use

Australia

No information is available on the introduction and industrial use of the chemicals in Australia.

International

International use information has been identified through the following:

- European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers
- Chemwatch (Galleria Chemical)
- Substances and Preparations in Nordic countries (SPIN) database
- European Commission Cosmetic Ingredients and Substances (CosIng) database
- The Good Scents Company (TGSC)
- United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary
- US National Library of Medicine's Hazardous Substances Data Bank (HSDB)
- ECHA (European Chemicals Agency) CLH report
- publicly available information including Safety Data Sheets (SDSs).

Internationally, the chemicals have reported cosmetic uses, including as:

- buffering agents (pH adjuster) in shampoos, conditioners, lotions and creams
- semi-permanent hair straightening agents
- anti-static agents in (non-colouring) hair products and other hair grooming aids.

Although glyoxylic acid is typically sold for formulation at a concentration of 50% w/v (in aqueous solution), the average maximum use level in cosmetic products (hair products) is reported to be 12% (ECHA 2017). The hair products containing glyoxylic acid are regarded as substitutes for straightening products containing formaldehyde and are known in the cosmetic industry as formaldehyde-free alternatives (Boga et al., 2014; EWG; REACH; TGSC). The carboxylate and aldehyde groups of glyoxylic acid react with the amine groups present in hair keratin resulting in the formation of stable bonds. This chemical is reported to be used in products at very low pH values, which have been considered more effective for the hair straightening process (Leite et al. 2018).

Glyoxylic acid has reported commercial uses, including:

- as a surface treatment
- in anti-scaling agents and corrosion inhibitors largely used in industrial manufacturing of cleaning and furnishing products.

Glyoxylic acid has reported site limited use as a chemical intermediate in the manufacture of chemicals, textile, leather or fur, metals, and fabricated metal products.

Glyoxylic acid has reported non-industrial uses in non-agricultural pesticides and preservatives (for example, in the manufacture of vanillin production in the flavour industry).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals.

Public

No specific controls are currently available for these chemicals.

Workers

Glyoxylic acid (CAS No. 298-12-4) is listed in the Hazardous Chemical Information System HCIS (Safe Work Australia, SWA) with the following hazard category and statements for human health:

- Eye damage – Category 1 (H318: Causes serious eye damage)
- Skin sensitisation – Category 1B (H317: May cause an allergic skin reaction).

These classifications are subject to note B.

'Note B: (Some substances (acids, bases, etc.) are placed on the market in aqueous solutions at various concentrations and, therefore, these solutions require different classification and labelling since the hazards vary at different concentrations. Entries with Note B have a general designation of the following type: 'nitric acid …%'. In this case the supplier should state the percentage concentration of the solution on the label. Unless otherwise stated, it is assumed that the percentage concentration is calculated on a weight/weight basis.)'

The chemical, glyoxylic acid, monohydrate (CAS No. 563-96-2) is not listed on the HCIS.

No specific exposure standards are available for these chemicals (SWA).

International regulatory status

Exposure standards

No specific exposure standards are available for these chemicals.

Health hazard information

Toxicokinetics

Absorption

Following oral administration of glyoxylic acid (CAS No. 298-12-4; as concentration of 50% w/v in aqueous solution), the chemical is reported to be absorbed from the gastrointestinal tract (GI) tract. The chemical is expected to be largely ionised at the pH value of the small intestine and expected to be mostly non-ionised at the low pH of the stomach. Although non-ionised chemicals are more readily absorbed than ionised chemicals, absorption after oral

exposure will mostly occur in the small intestine. There is minimal absorption in the stomach due to the small absorption area and less vascularisation in the stomach (REACH).

Absorption via passive diffusion (example by passage through aqueous pores or carriage through the epithelial barrier with the bulk passage of water) is due to a low molecular weight (74.04 g/mol) and log K_{ow} of -1.4 at 20 °C (REACH).

Restriction of passage through the lipid-rich environment of the stratum corneum is expected due to its high-water solubility (1.00E+06 mg/L at 25 °C) (despite molecular weight less than 100 Dalton). Based on read across from glycolic acid which has similar physicochemical properties to glyoxylic acid, dermal absorption will depend on a number of factors including pH, concentration, type and composition of the formulation (NICNAS 2000).

Inhalation exposure to the chemical is reported to be feasible due to the moderate vapour pressure (1.060 mm Hg at 25 °C) and general potential of aqueous products to form aerosols. Based on read across from glycolic acid, the chemical is expected to be readily absorbed following inhalation exposure (NICNAS 2000).

Metabolism

Glyoxylic acid occurs endogenously and is reported to be metabolised through several intermediate metabolic pathways. The major metabolic route of toxicological significance is the conversion to oxalic acid either by the liver peroxisome-specific glycolate (L-2-hydroxyacid) oxidase A), which has a broad substrate specificity that includes glyoxylate; or by lactate dehydrogenase (LDH) in the cytosol and interstitial tissue fluids. Physiologically relevant pathways that do not lead to toxicologically relevant metabolites include the formation of glycine by alanine: glyoxylate aminotransferase (AGAT), and the oxidation via formic acid to carbon dioxide and water.

Excretion

In a non-guideline rat study, carbon-14 labelled glyoxylic acid (0.06 mmol) was administered by i.p. injection together with sodium benzoate, where doses of 1 mmol of the labelled acid as the sodium salt with sodium benzoate were administered. The rate of oxidation indicated by the ^{14}C activity in carbon dioxide was studied at 0.5-hour intervals for 5 hours. Rates of oxalic acid and hippuric acid formation were measured in urine for 24 hours. The chemical was excreted at 16% as respiratory CO_2, 27.1% as oxalic acid, and 22% as hippuric acid in the urine (REACH).

Acute toxicity

Oral

Based on the data available data, glyoxylic acid has low acute oral toxicity.

In an acute oral toxicity study equivalent to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, Wistar rats (10/females/dose) were administered (gavage) a single dose of 1250, 2000, 3200, or 5000 mg/kg bw of the chemical at a concentration of 50% w/v in aqueous solution. Mortality was seen at all doses except the lowest dose. However, significant mortality was reported only at the highest doses of 3200 mg/kg bw (8 out of 10 animals died) and 5000 mg/kg (10 out 10 animals died). The oral median lethal dose (LD50) was reported to be 2528 mg/kg bw. Treatment related clinical effects reported in the animals that were deceased included ragged breathing, disturbance of equilibrium, cramps, and convulsion in the ventral position. Gross pathology findings at

necroscopy included a pale, white coloured small intestine in animals that were deceased. However, no abnormalities were reported in the animals that survived after the 14-day recovery period (REACH).

Dermal

Based on the data available, the chemicals are considered to have low acute dermal toxicity.

In an acute dermal toxicity study (equivalent to OECD TG 402) in male and female Sprague Dawley (SD) rats (5/sex/dose), a single dose of 2000 mg/kg bw of the chemical (as glyoxalic acid 50% w/v aqueous solution) was dermally applied to the clipped skin for 24 hours, under semi-occlusive conditions. No significant treatment related effects indicating skin irritation, or systemic effects or mortalities were reported. The dermal LD50 was reported to be >2000 mg/kg bw (REACH).

Inhalation

No data are available for the chemicals. Based on read across from glycolic acid, the chemical is expected to be readily absorbed following inhalation exposure and may be harmful by inhalation at high doses.

Other

In a limited non-guideline study, mice (10/sex/dose; unspecified strain) were administered doses of 250, 300 and or 500 mg/kg bw/day glyoxylic acid by i.p. injections for an unspecified timeframe. Mortality occurred within 30 minutes after a short convulsive period in the treated mice at the 300 mg/kg bw dose. No further study details were available (REACH).

Corrosion/Irritation

Skin irritation

Due to the acidic nature of glyoxylic acid (pKa 3.1) and high acid reserve for the 50% aqueous solution it might be expected that these chemicals may produce irritation effects on the skin. However, based on the in vivo data available glyoxylic acid is not considered a skin irritant.

In a dermal irritation study conducted according to OECD TG 404 (with deviations: shortened observation period of 72 hours, application area 2.5 cm^2), 6 male New Zealand white (NZW) rabbits were treated with glyoxylic acid (50% w/v aqueous solution) for 4 hours under semi-occlusive conditions. Observations were recorded at 24, 48 and 72 hours after exposure. The following mean scores for all 6 animals were reported for observations at 24, 48 and 72 hours: 0, 0, 0, 0, 0, 0.33 for erythema, and 0, 0, 0, 0, 0, 0 for oedema (maximum score 0 of 4). Slight erythema was reported in one animal but was determined to be barely perceptible and effects were completely reversible within 48 hours. Thus, the chemical was considered to not be irritating to the skin. No further treatment related effects were reported during the study period (ECHA2018a; ECHA2018b; REACH).

No irritation potential was seen in an acute dermal toxicity study in rats (OECD TG 402), performed with glyoxylic acid 50% v/v, aqueous solution (see **Acute toxicity: dermal** section)

Eye irritation

Based on the available data, the chemicals are considered to cause eye damage.

Glyoxylic acid is classified as hazardous in the as 'Serious eye damage - category 1' (see **Existing Australian regulatory controls** section). The data are consistent with this classification.

Due to the low pH value of glyoxylic acid, it can be expected that the chemicals may produce irreversible eye damage.

In a primary eye irritation study according to OECD TG 405 (with deviations), 0.1 ml of the glyoxylic acid (50% w/v aqueous solution) was instilled into the inferior conjunctival sac of the right eye of 6 male NZW rabbits. The left eye served as control. The eyes were washed out 4 seconds (3 animals) and 30 seconds (3 animals) after instillation and observed at 1, 24, 48, 72 hours and 7 days after application. The following mean scores (for all 6 animals) were reported at 24, 48 and 72 hours: corneal opacity 3.83/4, iritis 1.78/2, conjunctival redness 2.22/3, conjunctival discharge 1.83/3, and chemosis 3.94/4. Although individual scoring results are not documented in the study, the mean values imply that at least in 5/6 tested animals a corneal opacity of > 3 and response of iritis > 1.5 was obtained. The chemical was reported to be corrosive to the treated eyes of rabbits as effects were not reversible after the 7 days observation period. Due to the severe and irreversible eye effects (eye damage) reported, the study was terminated before 21 days. Severe effects such as grade 4 corneal opacity are not expected to fully reverse within 21 days The study was considered reliable and study deviations were attributed as a result of the severity of treatment related effects. These deviations include eyes of animals were reported to be washed out 4 secs and 30 secs after instillation (similar to left eye controls); animals were only evaluated once daily; no individual scoring results were reported; and treatment period was limited to 7 days (REACH; ECHA2018a, ECHA2018b).

Respiratory irritation

No data are available for the chemicals. In acute and repeated dose inhalation toxicity studies, with the structurally related glycolic acid, histopathological changes and clinical signs consistent with irritation of the respiratory tract were observed (NICNAS 2000).

Sensitisation

Skin sensitisation

Based on the available data, the chemicals are considered to be moderate skin sensitisers.

Glyoxylic acid is classified as hazardous 'Skin sensitisation – Category 1B.''. The data are consistent with this classification (see **Existing Australian regulatory controls** section).

In vivo

In a local lymph node assay conducted according to OECD TG 429 (with deviations and limitations), 5 female/dose Balb/C mice received topical application of glyoxylic acid (in acetone) at concentrations of 1.25, 2.5, 5, 10, 20 or 40% (v/v). It was not specified in the publication whether the dose levels expressed in percentages are for the 50% v/v glyoxylic test substance or if they are already re-calculated for 100% v/v substance. The reported stimulation indices (SI) were, 2.5, 10.7, 20.3 and 23.9 for concentrations of 5, 10, 20 or 40%,

respectively. The estimated concentration to produce a 3-fold increase in lymphocyte proliferation (EC3) was calculated to be 5.05% in the study. If the percentages were given for the 50% v/v glyoxylic test substance, the resulting estimated EC3 value would be 2.525%. It was also reported during the pre-screening test, 2/5 animals at the top 2 doses exhibited signs of irritation including ear swelling and redness post-exposure. Therefore, results at these doses may not be reliable. However, positive results (stimulation index (SI) ≥ 3) were obtained at 10% and results for all concentrations tested were concentration dependent. In addition, phenotypic analysis of the draining lymph nodes identified significant increases in B220+ cell populations at all concentrations tested. The correlation of immunophenotypic marker B220+ with sensitisation potential in the LLNA supports a true positive result. (REACH; Anderson et al., 2008; ECHA2018a, ECHA2018b).

In a non-guideline dermal sensitisation study (conducted according to Freund's Complete Adjuvant Test (FCAT) with open challenge), glyoxylic acid ((50% w/v in aqueous solution) was dermally applied to Pirbright white guinea pigs (15 males). The animals were exposed through induction: 10 intracutaneous injections over 14 days, followed by an epicutaneous, open challenge of 80% at 14 and 48 hours. After 24 hours of challenge treatment, it was reported that all animals (15/15) produced a positive skin sensitisation response (erythema) that was not reversible within 3 days, compared to controls indicating the skin sensitisation potential of the chemical. However, limited study data are available, and the above study was not reported to be reliable (REACH; Anderson et al., 2008; ECHA2018a, ECHA2018b, ECHA2018b)

In silico

Glyoxylic acid (in its aldehyde form) had protein binding alerts (Schiff base formers) for skin sensitisation based on its molecular structure as profiled (in silico) by the OECD QSAR Toolbox v4.2. The skin metabolism simulator indicated potential metabolism of dihydroxyacetic acid to glyoxylic acid (QSAR 2022; REACH). However, the knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 utilised, predicted the chemicals to be non-sensitisers.

Repeat dose toxicity

Oral

Based on the data available, the chemicals are not expected to cause systemic health effects following repeated oral exposure.

In a combined repeated dose/reproductive/developmental oral toxicity study (equivalent to OECD TG 422), male (10/dose) and female SD rats (15/dose) were administered the chemical as 50% w/v aqueous solution in diet at doses of 0, 2000 ppm, 6000 ppm, or 18000 ppm (equivalent to 0, 80, 240 and 730 mg/kg/day in females; and 0, 70 mg/kg/day, 200 mg/kg/day and 600 mg/kg/day in males, respectively. The animals were divided in 2 subgroups: toxicity subgroup: 5 males and 5 females/group and a reproduction subgroup: 5 males and 10 females/group. Reproductive subgroup females were exposed for approximately 6-8 weeks (from 14 days before pairing, during pairing period, gestation, littering and lactation period until day 4). Reproductive subgroup males were exposed for 14 days before pairing until approximately week 6. The exposure period for the toxicity subgroup animals was reported to be 5 weeks.

No significant adverse treatment related effects were reported. The no observed adverse effect level (NOAEL) for systemic toxicity for the chemical was reported to be 6000 ppm for males (equivalent to 200 mg/kg bw/day), the second highest dose tested based on the

statistically significantly reduced cumulative bodyweight gain among males at 18000 ppm (equivalent to 600 mg/kg/day). The NOAEL for females is reported to be at the highest dose 18000 ppm (equivalent to 730 mg/kg bw/day) (REACH).

Although the metabolite oxalic acid is nephrotoxic and caused effects in the testes (NICNAS 2014) there was no evidence of such effects including precipitation of calcium oxalate crystals in this study.

Dermal

No data are available for the chemicals.

Inhalation

No data are available for the chemicals.

Genotoxicity

Based on the data available, the chemicals are not considered to have genotoxic potential.

In vitro

In a bacterial reverse mutation test (according to OECD TG 471), the chemical was not mutagenic in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, TA 1538 and *Escherichia coli* WP2 at concentrations up to 10000 µg/plate, with or without metabolic activation (REACH).

In a mammalian cell gene mutation test (according to OECD TG 476) in mouse lymphoma L5178Y cells the chemical was not mutagenic at the thymidine kinase (*tk)* locus up to 150 µg/mL, with or without metabolic activation (REACH)

Positive results were reported in non-guideline bacterial reverse mutation assays with *S. typhimurium* TA 100, TA97, TA98 and TA104 with and without metabolic activation. Limited study details were available (REACH).

In vivo

In a GLP compliant mammalian erythrocyte micronucleus test (similar to OECD TG 474), CD-1 mice (4/sex/dose) were administered (gavage) 2 doses (24 hour interval) of 0, 183, 366, or 914 mg/kg bw of the chemical at a concentration of 50% w/v in aqueous solution. The reported incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups as compared to controls indicating a lack of clastogenicity (REACH).

In silico

Glyoxylic acid (in its aldehyde form) had an alert for in vitro mutagenicity (Ames test) (simple aldehyde) based on the molecular structure as profiled (in silico) by the OECD QSAR Toolbox v4.2 (OECD 2022). Both chemicals had an alert for in vivo mutagenicity (micronucleus) (H-acceptor pathway) based on the molecular structure as profiled (in silico) by the OECD QSAR Toolbox v4.2 (OECD 2022). The predicted metabolites had the same alert for in vivo but not in vitro mutagenicity. The knowledge based expert system DEREK Nexus version 6.0.1 utilised to predict the genotoxic potential of the chemicals did not match

any structural alerts or examples for (bacterial in vitro) mutagenicity. Additionally, the chemical structure did not contain any unclassified or misclassified features and was therefore, predicted negative for genotoxicity.

Carcinogenicity

No data are available for the chemicals. An alert (simple aldehyde) for genotoxic carcinogenicity based on the molecular structure as profiled (in silico) by the OECD QSAR Toolbox v4.2 (QSAR 2022; REACH) was indicated for chemicals (but not predicted metabolites). However, the knowledge based expert system DEREK Nexus version 6.0.1 utilised to predict the carcinogenic potential of representative chemicals in this group gave negative results.

Reproductive and development toxicity

Based on the data available, the chemicals are not expected to cause specific reproductive or developmental toxicity effects.

In a combined repeated dose/reproductive and developmental oral toxicity study (equivalent to OECD 422) previously described (see to **Repeated dose toxicity: Oral** section), SD rats (females: 10/dose; males: 5/dose) were administered the chemical in the diet for up to 7 weeks. No treatment related adverse effects on reproductive or developmental parameters were reported up to the highest dose tested. A reproductive and developmental NOAEL of 18000 ppm (equivalent to 600 mg/kg bw/day for males; and 730 mg/kg bw/day for females) was reported (REACH).

A reduction in the number of live pups per litter, and effects in the testes were observed in studies with the metabolite oxalic acid (NICNAS 2014). There was no evidence of such effects in this study.

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